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Fluoropolymer-based Emulsions for the Intravenous Delivery of Sevoflurane

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Background: **The intravenous delivery of halogenated volatile anesthetics has been previously achieved using phospholipid-stabilized emulsions, *e.g.*, Intralipid. However, fluorinated volatile anesthetics, such as sevoflurane, are partially fluorophilic and do not mix well with classic nonfluorinated lipids. This effect limits the maximum amount of sevoflurane that can be stably emulsified in Intralipid to 3.5% vol/vol. This is a significant limitation to the potential clinical use of Intralipid-based emulsions.**

Methods: **The authors prepared a 20% vol/vol sevoflurane emulsion using a novel fluorinated surfactant and tested its effectiveness and therapeutic index by administering it to male Sprague-Dawley rats *via* intravenous injection into the jugular vein. The median effective dose to induce anesthesia (ED_{50}), the median lethal dose (LD_{50}), and the therapeutic index (LD_{50}/ED_{50}) were determined. Anesthesia was measured by loss of the forepaw righting reflex.**

Results: **The ED_{50} and LD_{50} values were found to be 0.41 and 1.05 ml emulsion/kg body weight, respectively. These lead to a therapeutic index of 2.6, which compares favorably with previously determined values of emulsified isoflurane, as well as values for propofol and thiopental.**

Conclusions: **A novel semifluorinated surfactant was able to considerably increase the maximum amount of stably emulsified sevoflurane compared with Intralipid. These formulations can be used to rapidly induce anesthesia with bolus dosing from which recovery is smooth and rapid.**

THE intravenous delivery of halogenated volatile anesthetics has been of interest for more than 40 yr because of the possibility of improving on traditional methods of delivery. Direct injection into the bloodstream eliminates the time for the anesthetic to equilibrate with the lungs and leads to a more rapid onset of anesthesia. Initial instances of direct intravenous delivery of neat halothane, whether intentional or not, caused significant pulmonary damage and death in both animals and humans.[1–4] Later efforts successfully used fat emulsions as a means of delivery for halothane[5–7] and, more recently, isoflurane and sevoflurane.[8–10] Studies on these emulsions also showed that intravenous delivery of fluorinated volatile anesthetics can be used to produce preconditioning and thereby reduce the extent of myocardial infarction.[9] All of these examples have either used Intralipid (a phospholipid-stabilized soybean oil emulsion sold commercially) or directly used phospholipids as the emulsifier. However, fluorinated volatile anesthetics are partially fluorophilic, and they do not mix well with classic nonfluorinated lipids.[11] This property is evident in the limited concentrations of anesthetics that are soluble in Intralipid.[10]

Perfluorocarbon emulsions have been widely studied for use as blood substitutes.[12] The second-generation emulsion Oxygent (Alliance Pharmaceutical Corp., San Diego, CA) incorporates 30% by volume of perfluorooctyl bromide (perflubron). In an *in vitro* analysis, Cuignet *et al.*[13] demonstrated that the presence of Oxygent greatly increases the blood:gas partition coefficient of isoflurane, sevoflurane, and desflurane compared with Intralipid. Highly fluorinated compounds such as perfluorooctyl bromide are characterized by both lipophobicity and extreme hydrophobicity, the hallmark of fluorophilicity. The physical–chemical properties of organic molecules are deeply affected by the introduction of fluorine substituents to the point that highly fluorinated organic molecules can generate a new phase of liquid matter, usually referred to as a fluorous phase. This phase does not mix with both polar and nonpolar hydrogenated phases. As an example, perfluorooctyl bromide presents only a limited solubility in either water or hydrocarbons, but it is completely miscible with perfluorosolvents. For the same reason, highly fluorinated anesthetics such as isoflurane, sevoflurane, and desflurane prefer the environment provided by fluorophilic molecules such as perfluorooctyl bromide *versus* Intralipid. In addition, fluorinated surfactants have been shown to form highly stable perfluorocarbon–water emulsions with fluorinated compounds by significantly reducing the interfacial tension between the perfluorocarbon and water.[14,15]

The affinity of fluorinated anesthetics for fluorophilic molecules prompted the investigation of the emulsification of volatile anesthetics using a semifluorinated surfactant. In the current study, we demonstrate the successful induction of anesthesia in rats *via* intravenous

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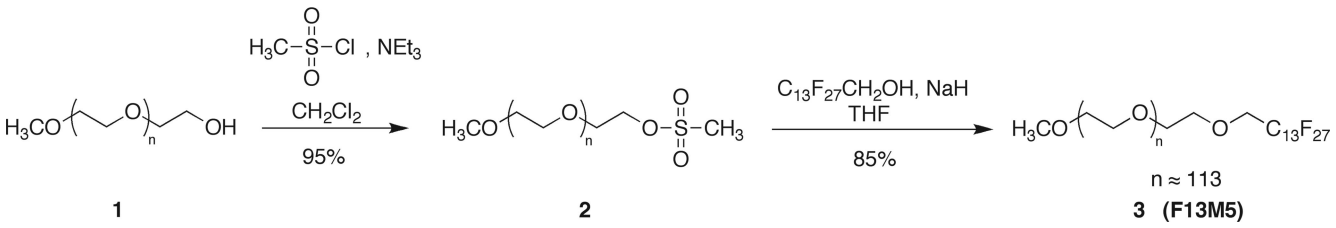

Fig. 1. Synthesis of the fluorosurfactant F13M5, used as the emulsifier.

delivery of sevoflurane, emulsified by the novel semifluorinated surfactant **3** (fig. 1; F13M5) and stabilized by perfluorooctyl bromide. The copolymer surfactant is composed by a monodisperse, large fluorophilic block ($C_{13}F_{27}$) attached to a poly(ethylene glycol) through an ether linkage. The large fluorous block allows an improved stabilization of fluorous emulsions compared with lipid formulations, while the ether linkages induce resistance to various forms of metabolism. Furthermore, we have determined the median effective dose (ED_{50}) and median lethal dose (LD_{50}) of such emulsions. This study thus demonstrates the successful emulsification of halogenated anesthetics using surfactants other than phospholipids.

Materials and Methods

All animal studies were conducted according to the guidelines laid out in the *Guide for the Care and Use of Laboratory Animals* and were approved by the University of Wisconsin Animal Care and Use Committee, Madison, Wisconsin.

Polymer Synthesis

A novel semifluorinated surfactant was synthesized for use as an emulsifier as indicated in figure 1. The synthesis starts with the activation of the hydroxyl functionality of polyethylene glycol monomethyl ether (molecular weight 5,000) with methanesulfonyl chloride. The resulting polymeric methanesulfonate ester is then coupled to 1H,1H-perfluoro-1-tetradecanol (SynQuest Laboratories, Inc., Alachua, FL) to afford the final product, F13M5, in high overall yield. The polymer nomenclature FXMY indicates that a certain polymer contains X number of perfluorocarbons and a monomethyl-poly (ethylene glycol) block of averaged molecular weight Y (in thousands g/mol).

Experimental Procedures

Polyethylene glycol monomethyl ether **1** (average molecular weight 5,000 g/mol), was purchased from Fluka (a brand of Sigma-Aldrich, St. Louis, MO) and lyophilized before use. Methanesulfonyl chloride (99.5%) and triethylamine (99.5%) were purchased from Sigma-Aldrich and used as provided. Methylene chloride (GC Resolv grade) and tetrahydrofuran (Optima grade) were purchased from Thermo Fisher Scientific, Inc. (Waltham, MA) and dried by flowing through alumina-containing columns. Anhydrous diethyl ether was purchased from EMD Chemicals, Inc. (San Diego, CA). 1H,1H-perfluoro-1-tetradecanol was purchased from SynQuest Labs. Dry NaH (95%) was purchased from Sigma-Aldrich. ^{19}F-nuclear magnetic resonance (NMR) and ^{1}H-NMR spectra were obtained on a Varian Inova spectrometer (Varian, Inc., Palo Alto, CA) operating at 400 MHz. High-pressure liquid chromatography chromatograms for product purity determination were obtained on a Gilson, Inc. (Middleton, WI) high-pressure liquid chromatography system with a Jordi FLP (Bellingham, MA) RP-DVB column with particle size of 5 μm and pore size of 1,000 Å, and detected with an evaporative light scattering detector from Gilson. The solvent gradient started at 10% MeCN/90% H_2O and increased to 100% acetonitrile over 20 min. The flow rate was 1 ml/min.

Polyethylene Glycol Monomethyl Ether Mesylate 2. Lyophilized polyethylene glycol monomethyl ether **1** (30.67 g, 6.1 mmol) was dissolved in anhydrous CH_2Cl_2 (200 ml) with mild heating. After cooling to room temperature, triethylamine (1.7 ml, 12 mmol) and mesyl chloride (0.7 ml, 9 mmol) were added, and the reaction mixture was stirred overnight under argon at room temperature. The precipitated salts were removed by vacuum filtration, and the filtrate was rotary evaporated to dryness. The remaining solid was taken up in $CHCl_3$ and purified through silica gel with $CHCl_3$, followed by 10:1 $CHCl_3$:methanol to remove any residual salts. The filtrate was evaporated to dryness and taken up in tetrahydrofuran (200 ml). Diethyl ether (250 ml) was added, and the solution was cooled in a refrigerator at 4°C for 30 min until precipitation was complete. The solid product was collected by vacuum filtration, dissolved in water, and lyophilized to yield polyethylene glycol monomethyl ether mesylate, **2**, as a white powder (27.4 g, 88% yield).

^{1}H-NMR $CDCl_3$ δ 3.09(s, 3H), 3.38(s, 3H),
3.46–3.83(m, 450H), 4.38(m, 2H)

Polyethylene Glycol Monomethyl Ether–Perfluorocarbon Conjugate 3 (F13M5). Mesylate **2** (8.14 g, 1.6 mmol) and 1H,1H-perfluoro-1-tetradecanol (2.789 g, 3.98 mmol) were dissolved in anhydrous tetrahydrofuran (500 ml) with mild heating. After cooling to room temperature, NaH (0.356 g, 14.8 mmol) was added. After

reflux for 48 h, the reaction was quenched with dropwise addition of water. The precipitated salts were removed by vacuum filtration. The filtrate volume was reduced by half by rotary evaporation, diethyl ether (250 ml) was added, and the solution was cooled until precipitation was complete. The solid was collected by vacuum filtration, taken up in $CHCl_3$, and flowed through silica gel with 10:1 $CHCl_3$:methanol to remove any residual salts. The filtrate was evaporated to dryness and taken up in tetrahydrofuran (200 ml). Diethyl ether (250 ml) was added, and the solution was cooled in a refrigerator at 4°C for 30 min until precipitation was complete. The solid product was collected by vacuum filtration, dissolved in water, and lyophilized to yield 14H,14H-perfluorotetradecane polyethylene glycol monomethyl ether, **3** (F13M5), as a white powder (7.8 g, 85%).

^{1}H-NMR $CDCl_3$ δ 3.38 (s, 3H), 3.46–3.83 (m, 450H), 4.05 (t, J = 13.6 Hz, 2H)

^{19}F-NMR ($CDCl_3$)δ −81.10 (t, J = 10.5, 3F), −120.13 (m, 2F), −122.01 (m, 16F), −123.01 (m, 2F), −123.78 (m, 2F), −126.45 (m, 2F)

Polymer purity (100%) was confirmed by high-pressure liquid chromatography. Retention time for semifluorinated surfactant **3** was 12.9 min.

Emulsion Preparation

Sevoflurane (Abbott Labs, N. Chicago, IL; 3.4 ml) and perfluorooctyl bromide (SynQuest Laboratories, Inc.; 1.7 ml) were added to an aqueous 0.9% NaCl solution (11.9 ml) of F13M5 (298 mg, 25 mg/ml), for a total volume of 17 ml. The two-phase mixture was homogenized with a low-energy mixer (Power Gen 500; Fisher Scientific, Hampton, NH) for 1 min at 21,000 rpm at room temperature. The crude emulsion was further homogenized under high pressure (5,000 psi, 1 min) using a Microfluidizer (model 110 S; Microfluidics Corp., Newton, MA) with the temperature maintained at 20.0°C with a cooling bath. The product emulsions of 20% (vol/vol) sevoflurane were stored in 15-ml sterile centrifuge tubes (Corning Inc., Corning, NY) at 4°C until use. Emulsions that were similar but contained isoflurane were also prepared. Initial studies employing tail vein injection used the isoflurane emulsions, and full dose–response studies employing implanted catheters used the sevoflurane emulsions.

The emulsions were sized by dynamic light scattering before use. For these measurements, the emulsions were mixed by inversion of the centrifuge tube to eliminate inhomogeneity due to either flocculation or sedimentation. The emulsions were then diluted by a factor of 300 by adding 10 μl of the emulsion to 2.990 ml NaCl, 0.9%. Sizing was done by dynamic light scattering (NICOMP 380 ZLS; Particle Sizing Systems, Santa Barbara, CA) with a 639-nm laser at a scattering angle of 90°. Each sample was run for 15 min, and all numbers are reported as gaussian volume weighted. The emulsions were only used if the average diameter was less than 350 nm. This cutoff was established to ensure consistent physical characteristics of the emulsion and to prevent acute toxicity that can develop with increased particle size.[16] In addition, the emulsion was filtered through a 0.45-μm nylon syringe filter. The final nanoemulsions are milky white.

Intralipid emulsions were prepared by emulsifying the corresponding amount of sevoflurane with commercially available Intralipid using the same methods and equipment described for the fluoroemulsions. Intralipid emulsions were not tested in animals because of the small amount of anesthetic that could be stably emulsified.

Animal Studies

Preliminary experiments performed to test for the efficacy of the anesthetic emulsions were performed using tail vein injections in adult male Sprague-Dawley rats (Harlan Sprague-Dawley, Inc., Indianapolis, IN) weighing approximately 300 g. For these studies, rats were restrained using a commercially available rodent restraint tube (Harvard Apparatus, Holliston, MA) during the injection.

For complete dose–response measurements, adult male Sprague-Dawley rats weighing approximately 300 g with a jugular catheter surgically implanted before purchase were used. Each dose was tested in five rats. The same rats were used on multiple days, but rats were only injected once a day to prevent any cumulative effects. Each rat was weighed so that the dose could be adjusted to be consistent with varying body weights. To determine the dose that was effective for anesthetizing 50% of the population (ED_{50}), groups composed of five rats each were injected with doses of emulsified anesthetic of 0.33, 0.36, 0.39, 0.43, 0.47, 0.55 and 0.62 ml/kg, respectively. With use of a syringe pump (11 plus; Harvard Apparatus), the rate was adjusted so that the bolus dose was always administered over 20 s regardless of volume. To determine the dose that was lethal for 50% of the population (LD_{50}), groups composed of five rats each were injected with doses of emulsified anesthetic of 0.945, 0.982, 1.018, 1.055, 1.091, and 1.127 ml/kg, respectively. Directly before the injections for the LD_{50} measurements, the rats were allowed to spontaneously breathe pure oxygen by being placed for 3 min in an induction chamber, to simulate the "preoxygenation" that is commonly used before induction in human pa-

tients. As a control experiment, emulsions containing only 10% perfluorooctyl bromide and no sevoflurane were prepared in the same manner as described in the Emulsion Preparation section. Five rats were injected with a volume of 1.091 ml/kg, equal to the sevoflurane emulsion volume at which 100% of the rats died.

To perform the injection, animals were restrained and the catheter wire port plug was removed and replaced with a flushing assembly (23-gauge hypodermic needle connected to a 1-ml syringe). The syringe plunger was gently drawn back until blood was seen in the tubing to ensure that there was no blockage of the catheter. If resistance was encountered, gentle pressure was applied to the plunger to dislodge the obstruction. When the catheter was completely filled with blood, it was connected to a syringe containing the experimental solution that was controlled by the syringe pump. The catheter was primed with 40 μl of solution (the volume of the catheter) so that flow into the body was immediate upon the start of the injection, and then the full injection was administered. After the injection was complete, the rat was rolled onto its back, with a loss of forepaw righting reflex considered inducement of anesthesia. If the righting reflex was lost, the right hind foot was pinched with a steel forceps to determine whether there was response to a painful stimulus. If the foot was not withdrawn, the pinch was applied every 5 s until there was a response. After injection, the rat was observed for 3 min, to measure the time required to regain the righting reflex and to observe for the presence of uncoordination (unsteady gait) or disorientation (repeated episodes of rearing and falling) during recovery. A "smooth recovery" was defined as resumption of grooming or purposeful exploration without evidence of uncoordination or disorientation during the recovery period. When recovery was complete (within 3 min in all cases), the catheter was flushed with 0.08 ml of a saline solution to remove the residual anesthetic emulsion and then refilled with 0.08 ml of a heparin-based fill solution. The sterile wire port plug was restored to seal the catheter.

Estimates for ED_{50} and LD_{50} were calculated through nonlinear regression, fitting data to a sigmoidal dose–response relation using the program Prism (version 4.0a; GraphPad Software, Inc., San Diego, CA). The data were fit to the equation

$$y = y_{min} + \frac{y_{max} - y_{min}}{1 + 10^{(\log ED_{50} - x) \times HillSlope}},$$

where x is the logarithm of concentration and y is the response.

The duration of anesthesia-*versus*-dose graph was made using DeltaGraph (version 5.6.1; SPSS Inc., Chicago, IL, and Red Rock Software, Inc., Salt Lake City, UT).

Results

In a set of preliminary experiments conducted using tail vein injections, isoflurane emulsions were found to induce anesthesia rapidly (within approximately 15 s, during the course of the injection) and for very brief durations (approximately 30 s). On recovery, animals showed no evidence of irritation, such as grooming or biting of their legs or tail, nor was there any obvious visual evidence of irritation at the injection site. Within approximately 1 min after the termination of injection, animals had returned to exploring their environment or grooming, with no evidence of uncoordination, disorientation, or residual sedation.

Because of the rapid onset, the ultrashort duration of action, and the need to repeatedly inject animals to establish ED_{50} and LD_{50} values, we used rats with catheters surgically implanted into the jugular vein and a syringe pump to deliver anesthetic emulsion for further studies. The dose–response curves for the ED_{50} and LD_{50} are presented in figure 2. The calculated ED_{50} value was 0.41 ml emulsion/kg body weight, with a 95% confidence interval from 0.37 to 0.45. This ED_{50} value corresponds to 0.081 ml pure sevoflurane/kg body weight based on an emulsion containing 20% vol/vol sevoflurane. The calculated LD_{50} value was 1.05 ml/kg body weight, with a 95% confidence interval from 1.03 to 1.07. This LD_{50} value corresponds to 0.21 ml pure sevoflurane/kg body weight based on 20% vol/vol

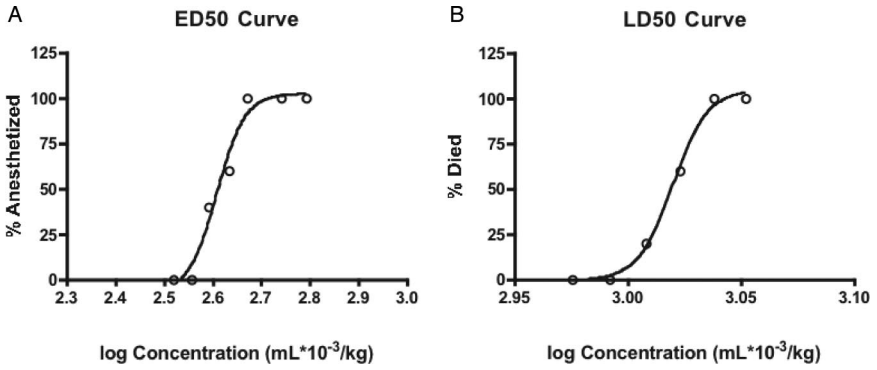

Fig. 2. Dose–response curves for the determination of the ED_{50} value for loss of righting reflex (*A*) and the LD_{50} value (*B*).

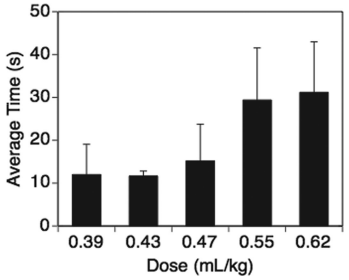

Fig. 3. Average duration of loss of righting reflex for rats that were anesthetized during the ED_{50} determination. *Error bars* indicate SDs.

sevoflurane emulsion. The therapeutic index (LD_{50}/ED_{50}) was calculated to be 2.6.

In the rats in which the righting reflex was lost, there was a response to the initial foot pinch (as indicated by a slight withdrawal of the foot) in all rats but one. One rat that was injected with the highest dose of 0.62 ml/kg did not respond to three foot pinches given at 5-s intervals but did respond to the fourth pinch.

Control experiments were performed by using anesthetic-free emulsions to test for effects of the fluoropolymer/perfluorocarbon emulsion. In these studies, there was no evidence of any anesthetic effects, gross neurologic deficit, or mortality. All rats were living 5 days later, giving no evidence of acute toxicity from circulating emulsions that had released the sevoflurane content.

In each case that anesthesia was induced, it occurred before the completion of the bolus dose, typically 17–20 s from the start. The average duration of anesthesia before recovery of the righting reflex is shown in figure 3. The duration was recorded at every concentration where anesthesia was induced, though by the nature of the ED_{50} experiments, some points had more rats anesthetized than others. The error bars indicate SDs, but the number of included points varies from two to five based on the number of rats in which anesthesia was induced.

The stability of the fluoroemulsions was checked with dynamic light scattering. Over a period of 2 months, emulsions containing 20% vol/vol sevoflurane, 10% vol/vol perfluorooctyl bromide, and 25 mg/ml fluoropolymer did not show phase separation, and the particle size was always in the submicron range. On the contrary, we found that Intralipid emulsions prepared during the same conditions used for the fluorous formulations and containing just 10% vol/vol sevoflurane were extremely unstable, and complete phase separation was easily detected within 1 day.

Discussion

We present evidence that a novel intravenous formulation of sevoflurane prepared using a fluoropolymer surfactant and perfluorocarbon is stable as an emulsion yet releases sevoflurane rapidly enough after intravenous injection that it can be used to induce anesthesia *in vivo*. The emulsification of volatile anesthetics in lipid formulations has previously been shown.[5–10] However, for any emulsion formulation to become clinically useful, the volume that can be stably emulsified must be significantly increased from current lipid formulations. The current study is the first that we know of to use an emulsifier other than phospholipids for a volatile anesthetic. The stable fluoropolymer-based emulsion that we tested here contained 20% vol/vol sevoflurane, which is almost a sixfold increase over the recently reported value of 3.46% vol/vol as the maximum solubility of sevoflurane in 30% Intralipid.[10] Furthermore, the instability of concentrated emulsions of sevoflurane in Intralipid presents a significant limitation to the clinical utility of intravenous delivery using Intralipid in human patients. On the contrary, the use of fluorosurfactants allows a considerably more convenient use of stable and concentrated emulsions of sevoflurane. Finally, it should be noted that while the studies described in this article are based on 20% sevoflurane formulations, more concentrated emulsions of this volatile anesthetic are also possible. We successfully prepared stable emulsions containing up to 30% sevoflurane.

While the use of sevoflurane emulsions has been demonstrated before, the present study also presents the first measurement of a therapeutic index for emulsified sevoflurane. Our calculated value of 2.6 compares reasonably well to previously published values of 3.2 and 3.1 for emulsified isoflurane[8,10] as well as 3.1 for propofol[10] and 2.2 for thiopental.[17] This finding suggests that a sevoflurane emulsion may provide an effective and convenient means of inducing anesthesia in human patients.

Doses that were near the ED_{50} for loss of righting reflex were effective for shorter periods of time than were higher amounts. In all instances, both the time to onset of anesthesia and the recovery of the righting reflex was rapid in comparison with other commonly used intravenous induction agents, such as thiopental and propofol.[10] The ability to rapidly induce or to deepen existing anesthesia by intravenous injection, combined with its rapid recovery profile, may prove beneficial under some circumstances. For example, it may be possible to achieve more stable hemodynamics by matching the depth of anesthesia with the intensity of stimulus during intubation, incision, or other brief but intense stimuli, such as insertion of cranial pins for neurosurgical procedures.

In conclusion, we have shown that a mixture of fluoropolymers and a fluorous additive such as perfluorooctyl bromide can stably emulsify 20% by volume of sevoflurane, a highly fluorinated volatile anesthetic. This is because of the increased affinity of the anesthetic for a fluorophilic surfactant. These formulations can be used to induce anesthesia with bolus dosing, from which

recovery is smooth and rapid. The observed difference between the measured ED_{50} and LD_{50} of our formulations suggests that these emulsions may be suitable for clinical use.

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