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Oxygen Tissue Saturation Is Lower in Nonsurvivors than in Survivors after Early Resuscitation of Septic Shock

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Background: **Growing evidence suggests that the microvascular dysfunction is the key element of the pathogenesis of septic shock. This study's purpose was to explore whether the outcome of septic shock patients after early resuscitation using early goal-directed therapy is related to their muscle tissue oxygenation.**

Methods: **Tissue oxygen saturation (Sto_2) was monitored in septic shock patients using a tissue spectrometer (InSpectra Model 325; Hutchinson Technology, Hutchinson, MN). For the purpose of this retrospective study, the Sto_2 values were collected at the first measurement done after the macrohemodynamic variables (mean arterial pressure, urine output, central venous saturation in oxygen) were optimized.**

Results: **After the hemodynamic variables were corrected, no difference was observed between the nonsurvivors and survivors, with the exception of pulse oximetry saturation (94% [92–97%] *vs.* 97% [94–99%], $P = 0.04$). The Sto_2 values were significantly lower in the nonsurvivors than in the survivors (73% [68–82%] *vs.* 84% [81–90%], $P = 0.02$). No correlations were found between the Sto_2 and Spo_2 ($P = 0.7$).**

Conclusions: **In septic shock patients, tissue oxygen saturation below 78% is associated with increased mortality at day 28. Further investigations are required to determine whether the correction of an impaired level of tissue oxygen saturation may improve the outcome of these patients.**

IN septic shock, guidelines recommend an early correction of mean arterial pressure, urine output, and central or mixed venous saturation in oxygen.[1] However, growing evidence suggests that the microvascular dysfunction is the key element in sepsis.[2] This dysfunction may be associated with impaired outcome.[3] At first glance, the correction of macrohemodynamics does not preclude whether or not the microvascular dysfunction continues.

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Near-infrared spectroscopy is a noninvasive monitoring, providing real-time feedback.[4] Near-infrared spectroscopy monitors only vessels with a diameter of less than 1 mm because the high concentration of blood in arteries and veins makes photon emergence unlikely. Near-infrared light (600–800 nm) easily crosses biologic tissues and is absorbed by hemoglobin, myoglogin, and oxidized cytochrome, as described elsewhere.[5] This tool can quantify microvascular dysfunction in patients with septic shock.[6]

One can hypothesize that near-infrared spectroscopy can detect a potential microvascular dysfunction in the patients adequately resuscitated from a macrohemodynamic standpoint. The purpose of this study was to explore whether the outcome of the septic shock patients after early resuscitation using early goal-directed therapy was related to their muscle tissue oxygenation.

Materials and Methods

This study was retrospectively conducted in a 16-bed intensive care unit of an 800-bed university hospital (Hôpital Nord, Marseille, France). Informed consent and approval by the Ethics Committee were waived due to the observational nature of the study.

Patients

Septic shock was defined according to the criteria of the International Sepsis Definitions Conference.[7] All patients received fluid expansion (crystalloids or 6% hydroxyethyl starch) and then required norepinephrine to raise mean arterial pressure to 65 mmHg or more.[1] All patients received broad-spectrum antibiotic coverage, usually a β-lactam and a quinolone. Vancomcyin was added when oxacillin-resistant staphylococci were suspected. All patients needed mechanical ventilation and sedatives because of acute respiratory failure. According to previously conducted studies, 50 patients with septic shock were expected within a 1-year period. Thus, all the patients with septic shock were included during a 1-year period (2007).

Measurements

Heart rate, mean arterial pressure, oxygen plethysmography, and end-tidal carbon dioxide were continuously monitored (Moniteur Patient Intellivue MP 70; Philips, Andover, MA). All patients had an arterial catheter and a central venous catheter placed through the subclavian vein. The arterial and venous catheters were connected

to a Picco-Plus monitor (Pulsion Medical Systems, Munich, Germany) in the patients in whom vascular accesses made it possible to insert this monitoring system. This monitoring is based on the transpulmonary thermodilution technique and arterial pulse contour analysis.[8] An indwelling urinary catheter was inserted in each patient. Urine was collected *via* a urinometer (Curity 0123; Kendall, Hands, United Kingdom). The following variables were prospectively collected: heart rate, mean arterial pressure, central venous saturation in oxygen ($Scvo_2$), pulse pressure variations if its measure seemed relevant to the attending physician (sinusal rhythm, no right heart failure, controlled ventilation), cardiac index if available, lactate plasma level, pulse oximetry saturation (Spo_2), hemoglobin, creatinine plasma concentration and urine output. Demographic data, severity score (simplified acute physiology score II),[9] and sedation score (Ramsay score)[10] were retrospectively collected. Our local protocol was aimed at correcting macrohemodynamic variables (mean arterial pressure, urine output, $Scvo_2$). Initial resuscitation consisted of intravenous fluid targeted to achieve pulse pressure variations below 13% in the patients with equipment.[11] If the patients were not equipped, echocardiography (respiratory variation in inferior vena cava diameter) analysis and passive leg raising (pulse pressure variations below 10%) were used.[12,13] The fluid resuscitation was stopped at the discretion of the attending if pulmonary edema was suspected. Norepinephrine dosage was adjusted to achieve a mean arterial pressure of at least 65 mmHg or to maintain urine output above 0.5 $ml \cdot kg^{-1} \cdot h^{-1}$.[14] After the mean arterial pressure and preload were optimized, if the $Scvo_2$ was less than 70%, dobutamine was added at an initial dose of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Ventilatory parameters were adjusted to raise arterial oxygen saturation more than 90%, and blood hemoglobin level was raised to more than 8 g/dl in patients with acute anemia.

Tissue Oxygenation Measurements

From 2006, tissue oxygen saturation (Sto_2) of the patients with septic shock was monitored in routine by using a tissue spectrometer (InSpectra Model 325; Hutchinson Technology, Hutchinson, MN). The device uses reflectance mode probes to measure scattering light reflected at some distance from where the light is transmitted into the tissue. The maximum depth of the tissue sample was estimated to equal half the distance between the probe's sending and receiving fibers.[15] We used probe spacing of 15 mm. A light-scattering calibrator was used to normalize the tissue spectrometer during startup of the system and before each measurement. Sample measurement signals were updated every 3.5 s.

For the purpose of the study, the Sto_2 values were collected at the first measurement done after the macrohemodynamic variables seemed optimal according to the decision of the attending physician. Briefly, preload was optimized (pulse pressure variations below 13% or lack of response to passive leg raising or no respiratory variations of the inferior vena cava diameter or pulmonary edema), mean arterial pressure was above 65 mmHg, urine output was above 0.5 ml/kg of body weight (except in the patients with acute renal failure), and the $Scvo_2$ was at 70% or more. At the measurement time, at least three of these aims had to be achieved in all patients. The near-infrared spectroscopy probe was placed on the clean skin of the thenar eminence. After a 3-min period to stabilize the near-infrared spectroscopy signal, the value of Sto_2 was recorded. A brief clinical assessment was performed by assessing the capillary refill time (less than 2 s) and the temperature at the level of the big toe (cold or hot). This assessment was done by two investigators (Drs. Blidi and Meyssignac).

To ensure that the data are not unique to the thenar eminence and not representative of the rest of the body, we included a second cohort of patients with septic shock after the macrohemodynamic variables were optimized as previously described. In this cohort, the values of Sto_2 were successively recorded at three sites: thenar, deltoid, and masseter.

Statistics Analysis

Statistical calculations were performed using the software package SPSS 15.0 (SPSS Inc., Chicago, IL) For continuous and ordinal variables, data were expressed as median with interquartile range (25–75% quartiles). For dichotomous variables, percentages were calculated. Comparisons between two groups (survivors and nonsurvivors) were performed with the Mann–Whitney U test. Comparisons of percentages were performed with the Fisher exact test. Comparisons of two continuous variables were performed using a linear regression. Comparisons between the three groups of the second cohort were made using the Kruskal-Wallis test. Discrimination of values was assessed with the receiver operating characteristic analysis. Sensitivity and specificity were also computed. All comparisons were two-tailed, and $P < 0.05$ was required to exclude the null hypothesis.

Results

Forty-two consecutive patients with septic shock were included in the study. Their characteristics are shown in table 1. Mortality at day 28 occurred in 13 (31%) patients (table 1). Three patients (23%) did not survive on day 3. The objectives of mean arterial pressure, urine output, and $Scvo_2$ were achieved in 42 (100%), 36 (86%), and 35 (84%) patients, respectively. After the hemodynamic variables were optimized, no difference was observed between the survivors and nonsurvivors, with the exception of Spo_2, which was significantly lower in the nonsurvivors than in the survivors (94% [92–97%] *vs.*

Table 1. Characteristics of the 42 Patients Included in the Study

	Survivors (n = 29)	Nonsurvivors (n = 13)	Entire Cohort (n = 42)
Female sex	9 (31)	4 (30)	13 (31)
Age, yr	59 (40–67)	60 (55–73)	59 (52–67)
Body mass index, kg/m^2	24 (21–29)	23 (22–24)	24 (22–28)
Simplified acute physiology score II	47 (37–54)	58 (42–63)	47 (38–58)
Creatinine plasma levels, μmol/l	96 (66–175)	111 (62–144)	96 (66–172)
Ramsay score	5 (3–6)	5 (4–6)	5 (3–6)
Source of septic shock			
Lungs	13 (45)	7 (54)	20 (48)
Intraabdominal	13 (45)	5 (38)	18 (43)
Urinary tract	2 (7)	0 (0)	2 (5)
Skin	0 (0)	1 (8)	1 (2)
Cerebrospinal fluid	1 (3)	0 (0)	1 (2)

No difference was observed between the survivors and the nonsurvivors. Data are presented as median (interquartile range) and number of patients (percentage).

97% [94–99%], $P = 0.04$) (table 2). Clinically, 22 (77%) of the survivors had a capillary refill time of less than 2 s, as compared with 13 (77%) of the nonsurvivors ($P = 1.00$). The big toe temperature was hot in 18 (63%) survivors and 8 (61%) nonsurvivors ($P = 0.7$). Interestingly, the Sto_2 values were significantly lower in the nonsurvivors than in the survivors (73% [68–82%] *vs.* 84% [81–90%], $P = 0.02$) (fig. 1).

A receiver operating characteristic analysis confirmed that Sto_2 was significantly associated mortality with an area under the curve at 71% (52–91%, $P = 0.03$) (fig. 2). This association was not found for $Scvo_2$, lactate plasma level, and norepinephrine dosage (fig. 2). A threshold of Sto_2 at 78% was associated with a sensitivity of 61% and a specificity of 87%. Nine (64%) patients whose Sto_2 was

Table 2. Hemodynamics of the Patients According to Their Survival

Variables	Survivors (n = 29)	Nonsurvivors (n = 13)	*P* Value
Heart rate, beats/min	100 (85–114)	94 (88–115)	0.4
Mean arterial pressure, mmHg	79 (72–87)	80 (71–84)	0.5
Urine output, ml/h	80 (40–100)	50 (32–80)	0.3
Pulse oxygen saturation, percentage	97 (94–99)	94 (92–97)	0.04
Pulse pressure variations,* percentage	9 (7–12)	8 (4–9)	0.3
Cardiac index,* (l/m^2)	3.8 (3.1–4.2)	4.1 (3.4–4.3)	0.9
Oxygen central venous saturation, percentage	78 (72–84)	79 (71–85)	0.9
Lactate plasma level, mmol/l	2.3 (1.4–2.9)	2.5 (1.5–4.7)	0.1
Hemoglobin, g/dl	9.1 (8.6–11)	9.1 (8.6–11)	0.9
Norepinephrine, $\mu g \cdot kg^{-1} \cdot min^{-1}$	0.4 (0.1–1.1)	1.0 (0.5–2.0)	0.2
Norepinephrine duration, h	36 (18–56)	24 (14–61)	0.5
Dobutamine, percentage of patients	3 (10)	1 (10)	1

* Data were available in 30 (70%) patients. Data are presented as median (interquartile range) and number of patients (percentage).

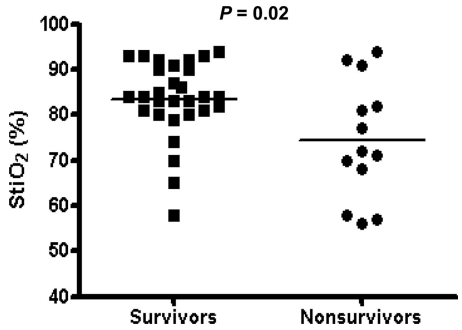

Fig. 1. Individual values of oxygen tissue saturation (Sto_2) are given for the survivors and nonsurvivors at day 28. *Horizontal lines* = median.

below 78% did not survive, as compared with five (36%) patients with the Sto_2 equal to or above 78% ($P = 0.002$).

Next, we searched for correlations between the Sto_2 and other variables. The Sto_2 was not correlated with the Spo_2 (fig. 3A), $Scvo_2$ (fig. 3B), or urine output (fig. 3C). There was also no correlation with mean arterial pressure ($P = 0.7$, $R^2 = 0.02$), cardiac index ($P = 0.2$, $R^2 = 0.03$), hemoglobin ($P = 0.8$, $R^2 = 0.02$), Ramsay score ($P = 0.2$, $R^2 = 0.02$) and norepinephrine dosage ($P = 0.9$, $R^2 = 0.02$). In contrast, the lactate plasma level was correlated with Sto_2 (fig. 3D).

Finally, in a new cohort of nine patients, we tested three distinct sites: thenar, masseter, and deltoid. Briefly, the two cohorts were similar in age (54 [40–59] *vs.* 59 [51–69] yrs, $P = 0.3$), sex ratio (33 *vs.* 33%, $P = 1$), SAPS II (50 [43–53] *vs.* 47 [38–58], $P = 0.8$), mean arterial pressure (84 [71–85] *vs.* 80 [72–85] mmHg, $P = 0.9$), urine output (50 [45–120] *vs.* 60 [40–100] $ml \cdot kg^{-1} \cdot h^{-1}$, $P = 0.5$), and $Scvo_2$ (76 [73–82] *vs.* 78 [71–84] %, $P =$

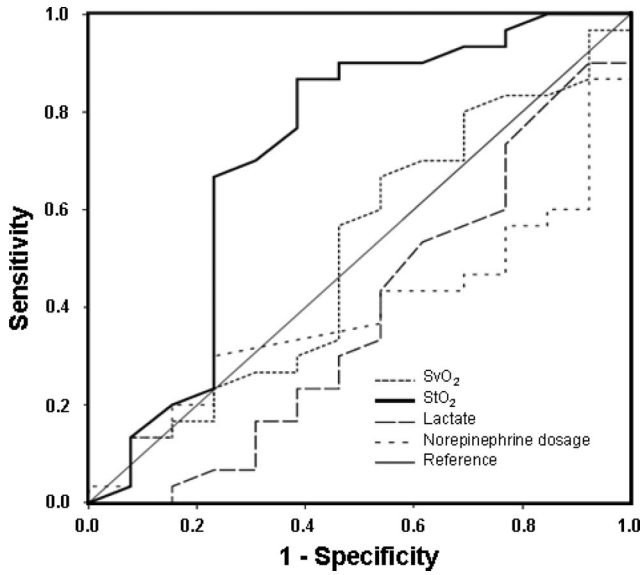

Fig. 2. Receiver operating characteristic curves. Tissue oxygen saturation (Sto_2), central venous saturation in oxygen ($Scvo_2$), lactate plasma level, and norepinephrine dosage according to survival. The areas under the curves are 71% (52–91%, $P = 0.03$), 56% (31–70%, $P = 0.9$), 38% (19–58%, $P = 0.1$), and 39% (22–56%, $P = 0.2$), respectively.

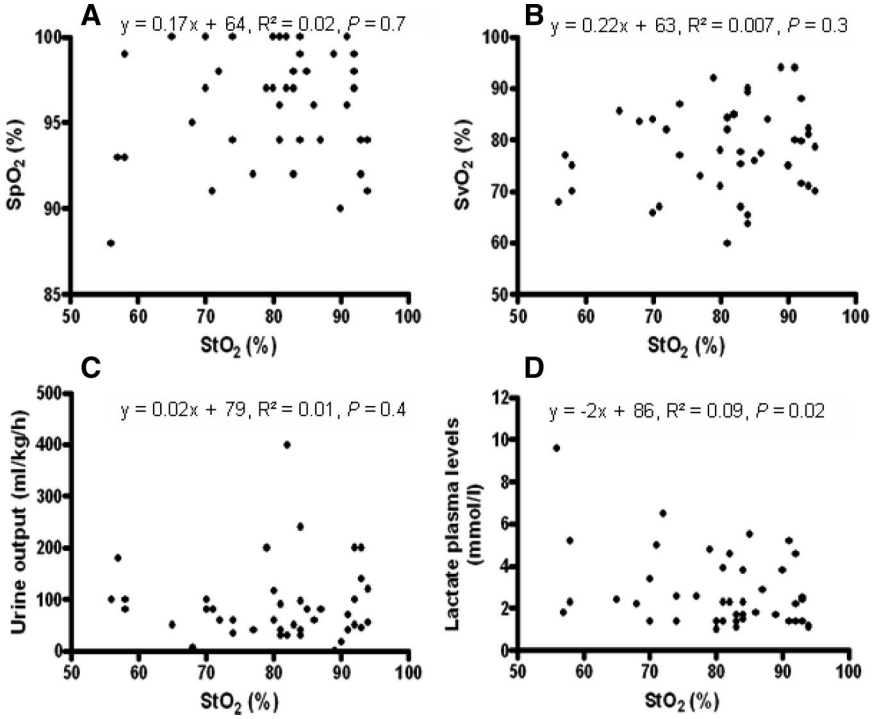

Fig. 3. Relationship between tissue oxygen saturation (Sto_2) and hemodynamic variables in the 42 patients with septic shock. (*A*) Pulse oximetry saturation (Spo_2) ($P = 0.7$). (*B*) Central venous oxygen saturation (Svo_2) ($P = 0.3$). (*C*) Urine output ($P = 0.4$). (*D*) Lactate plasma level ($P = 0.02$).

0.9). Sto_2 measured at the thenar eminence did not differ between the two cohorts (84 [80–89] *vs.* 78 [71–84] %, $P = 0.4$). No difference was found among the three sites of measurement (84 [80–89] *vs.* 89 [81–90] *vs.* 85 [78–90] %, $P = 0.7$).

Discussion

Our results show that, in a real-life study, after the macrohemodynamic variables were optimized, the Sto_2 of the nonsurvivors at day 28 was significantly lower than that of the survivors. A value of Sto_2 below 78% was associated with an increased risk of mortality. With the exception of plasma lactate levels, this variable was not correlated with the other markers of arterial oxygenation. As a result, this monitoring can provide an easy and direct tool to assess the risk of mortality in septic shock patients. In contrast, the impact of treatment aimed at correcting the Sto_2 should be investigated in future studies.

At the bedside, it is challenging to identify the microcirculation dysfunction. In the current study, the clinical assessment using capillary refill time and big toe temperature did not provide relevant information. Several methods have been reported to assess the microvascular blood flow.[16] Intravital microscopy is considered the standard for *in vivo* investigation of the microcirculation. This technique can be used for investigation of thin tissues that allow transillumination, whereas fluorescent dyes must be used to allow epiillumination of thicker organ surfaces. Unfortunately, the use of dyes in humans is hindered by safety concerns. Thus, intravital microscopy studies have been limited to observation of nail fold capillaries that can be observed without using dyes. Other techniques like laser-Doppler flowmetry, orthogonal polarization spectral imaging, and the sidestream dark field imaging are of major interest but remain difficult to use in real-life conditions. Our approach was to give priority to being noninvasive, being user-friendly, providing real-time feedback, and influencing mortality. The use of near-infrared spectroscopy responded to these specifications.

In a previously published study, the same monitoring detected altered recovery after an ischemic challenge in patients with septic shock.[5] The presence and persistence of such alterations in the first 24 h of sepsis were associated with impaired outcome. However, this technique consists on stopping arterial blood flow by inflating the cuff to 50 mmHg above the systolic arterial pressure. After 3 min of ischemia, cuff pressure is released, and Sto_2 is recorded continuously for another 3-min period. The slope of the increase in Sto_2 and the difference between the maximum Sto_2 value during hyperemic phase and the baseline Sto_2 are calculated. Although this technique provides interesting results, our approach offers a direct and continuous measurement available at the bedside. In addition, different sites of measurements seem available without affecting the significance of results.

The association between Sto_2 and outcome has already been reported in trauma patients.[17,18] In the emergency room, the information about Sto_2 allows for discriminating the patients who would later go on to develop multiorgan dysfunction syndrome or die.[17] In the current study, the Sto_2 also discriminates the patients with

poor outcome. The univariate analysis shows that the Spo_2 is lower in the nonsurvivors than in the survivors. One may hypothesize that Sto_2 is mainly dependent on Spo_2. However, no correlation was found between the Sto_2 and Spo_2. This result is in agreement with an experimental study, concluding that muscle tissue does not show changes reflecting a greater deoxygenation during acute hypoxia.[19] As a result, the monitoring of Sto_2 provides information about tissue oxygenation, which is independent of arterial oxygenation.

The patients with Sto_2 below 78% are at increased risk of mortality. No specific intervention was conducted regarding the correction of the low values of Sto_2. The goal of our protocol was aimed at correcting low $Scvo_2$. The $Scvo_2$ was above 65% in all patients but one. Six patients had values ranged from 65% to 70%. The prognosis value of this variable has been shown in the early phase of the management of patients with severe sepsis.[20,21] However, its relevance remains unknown after the patients are resuscitated. According to our study, with the exception of a type 2 error, the accuracy of Sto_2 to predict mortality seems superior to that of $Scvo_2$. In addition, our findings confirm previous studies in which the correlation between the two variables is poor or lacking.[22,23] However, we cannot conclude that the correction of Sto_2 above 78% would be an efficient measure to improve outcome.

Several limitations should be acknowledged. The study is of a small number of subjects at a single timepoint. The interpretation of nonsignificant results can result from a lack of power. Thus, it is difficult to discern between nonmeaningful differences existing *versus* lack of power to detect them. Use of eminence thenar may raise some issues. Indeed, the measurements may reflect changes in skin circulation at a depth of 7.5 mm. One can argue that this circulation is not representative of other circulations in our patients. To reduce this uncertainty, we tested three distinct sites in nine other patients: thenar, masseter, and deltoid. No difference was observed among the three sites, indicating that our results may be replicated by using other sites of measurement. However, in healthy volunteers, Sto_2 determined from deep muscle, not thenar eminence, was an indicator of central hypovolemia.[24] Thus, new technologies can improve the relevance of measurements. The use of 25-mm probes, instead of 15 mm, can also affect the results because the presumed depth of penetration is half of the path length.[18] This specific point requires future investigations. Finally, we did not explore Sto_2 change over time because the study was aimed at assessing the microcirculation at a specific time. One should admit that this did not improve outcome even though resuscitation increased Sto_2. However, the dynamic changes of Sto_2 over time are probably an interesting field of experimentation.

In conclusion, after the macrohemodynamic variables were optimized, the monitoring of Sto_2 can discriminate the patients at high risk of mortality. We determined that a Sto_2 below 78% is associated with an increased mortality. The impact of possible therapeutic aimed at increasing the Sto_2 was not explored in the current study. There is a need of further investigations to test such hypothesis.

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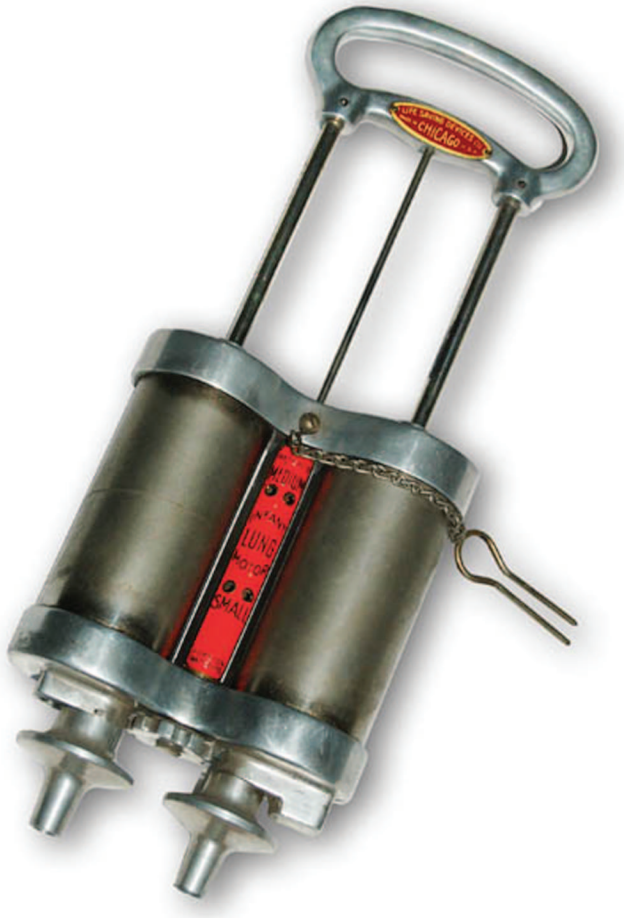
ANESTHESIOLOGY REFLECTIONS

The Infant Lungmotor



During and after World War I, Chicago's Life Saving Devices Company promoted its "Infant Lungmotor" for resuscitating young victims of drowning, smoke inhalation, and birth asphyxia. During such crises, an assistant would apply the device's facemask to the apneic infant as the lead resuscitator would hand-pump air through two lengths of metal tubing connecting the distal end of the Lungmotor to the double-nippled mask. Air or oxygen volume delivered per "Lungmotor breath" could be reduced by inserting the attached piston-limiting pin into slots designated for "SMALL"- or "MEDIUM"-sized infants. By 1928, Yale physiologist Yandell Henderson would record in *JAM*A that these Lungmotors were "inevitably applied neither gently nor moderately." (Copyright © the American Society of Anesthesiologists, Inc. This image appears in color in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

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