Oxygen

- The most widely used drug for the treatment of respiratory insufficiency.
- It is primarily aimed to avoid the harmful effects of hypoxia on the central nervous system and other organs.
- In newborns and preterm infants is even needed to avoid hyperoxia:
  - immaturity of the lungs;
  - immaturity of the antioxidant system;
  - demonstrated relation to Bronchopulmonary Dysplasia (BPD)[1], Retinopathy of Prematurity (ROP)[2] and Oxidative Stress[3].

1. Saugstad OD. *Biol Neonatol* 1998;87:819-24.
2. Avery G, et al. *Clin Perinatol* 1988;15:917-28.
3. Bonta VW, et al. *Pediatr Res* 1977;11:754-757.

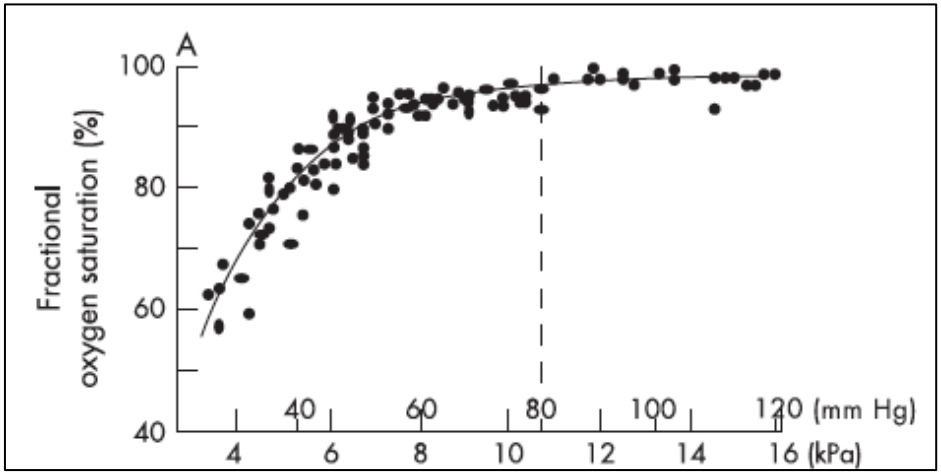
How to choose the right Sat.O_2 ?

REVIEW

Optimum oxygen therapy in preterm babies

W Tin, S Gupta

- The relationship between fractional oxygen saturation measured with a pulse oximeter and arterial partial pressure of oxygen (pO_2) in mmHg and kPa.



ROP occurred more often when the transcutaneous reading reached or exceeded 80 mmHg (10.7 kPa) in the first 4 weeks of life

Tin W, et al. *Arch Dis Child Fetal Neonatal Ed* 2007;92:F143

O_2 in Delivery Room

Resuscitation of Preterm Neonates With Limited Versus High Oxygen Strategy

Population: 24-34 weeks GA resuscitated in DR
Intervention: Low O_2 start with room air →

Control: High O_2 start with FiO_2 100%
then target to SpO2 84-95%

Outcome: Total hydroperoxide, biological antioxidant potential, oxidative balance ratio; DR intervention, respiratory support, short term morbidities

TABLE 1 Targeted Preductal Spo_2 After Birth

Time	Saturation Range
1 min	60%–65%
2 min	65%–70%
3 min	70%–75%
4 min	75%–80%
5 min	80%–85%
10 min	85%–94%

Kapadia VS, et al. Pediatrics 2013;132;e1488

- **CONCLUSIONS:** Low O_2 is feasible and results in less oxygen exposure, lower oxidative stress, and decreased respiratory morbidities and thus is a reasonable alternative for resuscitation of preterm neonates in the delivery room.

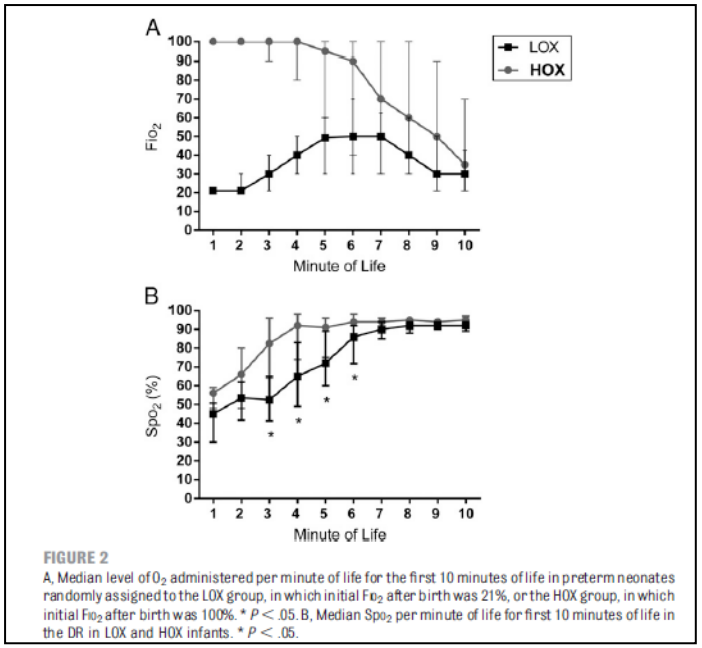
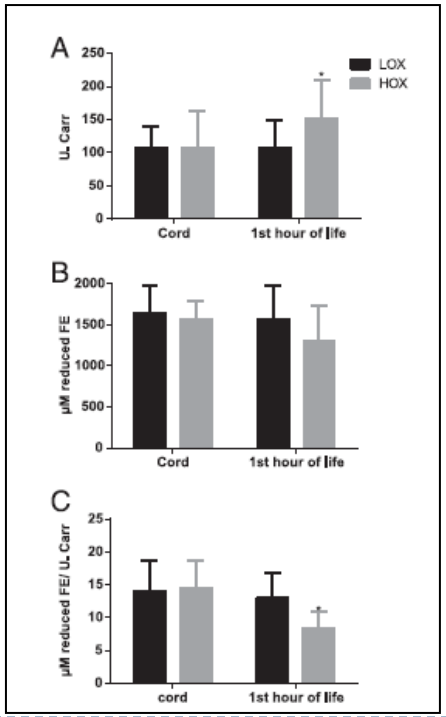


FIGURE 2
A, Median level of O_2 administered per minute of life for the first 10 minutes of life in preterm neonates randomly assigned to the LOX group, in which initial FIO_2 after birth was 21%, or the HOX group, in which initial FIO_2 after birth was 100%. * $P < .05$. B, Median SpO_2 per minute of life for first 10 minutes of life in the DR in LOX and HOX infants. * $P < .05$.



Total hydroperoxide

Biological antioxidant potential

Oxidative balance ratio

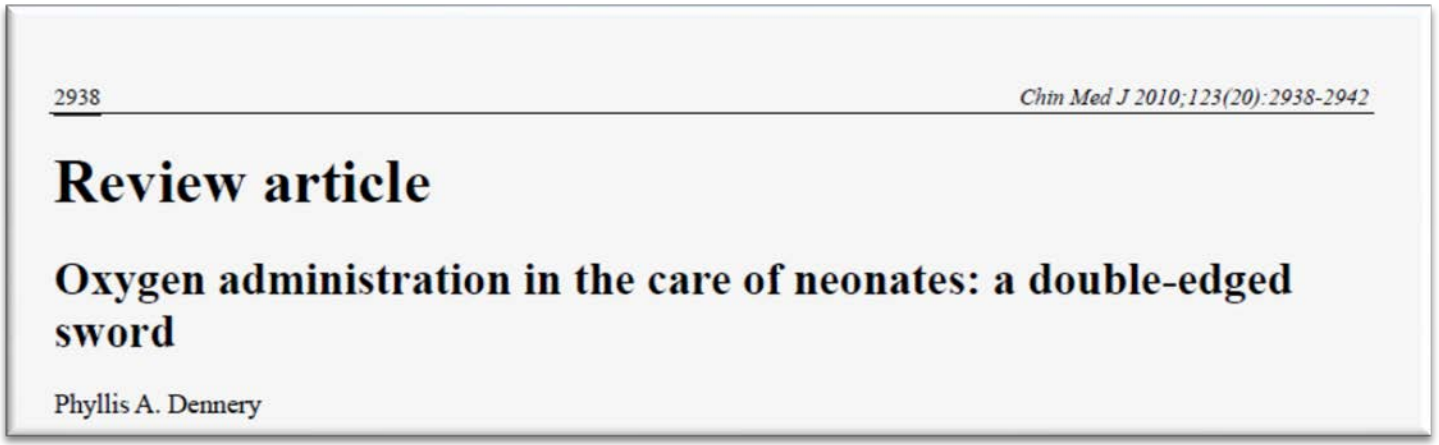
O_2 in acute phase

European Consensus Guidelines on the Management of Neonatal Respiratory Distress Syndrome in Preterm Infants – 2013 Update

- In preterm babies receiving oxygen the saturation target should be between 90-95% (B)
- After giving surfactant a hyperoxic peak should be avoided by rapid reduction in FiO_2 (C)
- Fluctuation in $SatO_2$ should be avoided in the postnatal period (C)

Sweet DG, et al. *Neonatology* 2013; 103:353

O_2 during routinary care



2938 *Chin Med J 2010;123(20):2938-2942*

Review article

Oxygen administration in the care of neonates: a double-edged sword

Phyllis A. Dennery

- In preterm infants, we must carefully monitor Oxygen saturations and keep these at less than 94% to prevent adverse pulmonary consequences such as BPD and to prevent ROP.
- Nevertheless we must prevent desaturations below 80-85% to prevent adverse consequences to the brain such as cerebral palsy.

The Journey Towards Lung Protective Respiratory Support in Preterm Neonates

Thomas M. Berger Matteo Fontana Martin Stocker

Table 2. Main findings of trials evaluating low (85–89%) versus high (91–95%) target oxygen saturations in extremely preterm infants [62–65]

Trial [year published]	Population studies	Subgroup n	Randomization SaO_2 target	Outcomes				
				death	BPD	ROP	NEC	death or NDI
SUPPORT [2010]	24 0/7–27 6/7 weeks	all (1,316)	low high	19.9% 16.2% p = 0.04	37.6% 46.7% p = 0.002	8.6% 17.9% p < 0.001	11.9% 10.8% n.s.	
SUPPORT [2012]	24 0/7–27 6/7 weeks	all (1,234)	low high	22.1% 18.2% p = 0.046	37.0% 39.7% n.s.	8.6% 17.4% p < 0.001	8.8% 8.6% n.s.	30.2% 27.5% n.s.
BOOST II [2013]	<28 0/7 weeks	all (2,448)	low high	19.2% 16.6% n.s.	35.6% 40.0% n.s.	10.6% 13.5% p = 0.045	10.4% 8.0% p = 0.04	
BOOST II	<28 0/7 weeks	revised algorithm (1,187)	low high	23.1% 15.9% p = 0.002	35.6% 40.8% n.s.	9.4% 11.4% n.s.	8.7% 6.2% n.s.	
COT [2013]	23 0/7–27 6/7	all (1,201)	low high	16.6% 15.3% n.s.	31.8% 33.0% n.s.	12.8% 13.1% n.s.	12.3% 9.3% n.s.	51.6% 49.7% n.s.
COT [2013]	23 0/7–27 6/7	revised algorithm (538)	low high	16.8% 14.1% n.s.	n.a. n.a. n.a.	n.a. n.a. n.a.	n.a. n.a. n.a.	52.6% 46.6% n.s.

n.s. = Not significant; n.a. = not available.

Neonatology 2013;104:265

It is probably safe (to current knowledge)

Nevertheless, for the time being, it seems prudent to target $SatO_2$ between 90 and 95% while avoiding extreme oxygenation levels (both hypoxia and hyperoxia)

- Bancalari et al, JAMA 2013;309:2161-2162;
- Polin RA et al, NEJM 2013;368:2141-2142

In conclusion, in babies <28 weeks' gestational age low saturation targets (85–89%) until 36 weeks postmenstrual age are associated with more deaths and more NEC, higher saturation targets (91–95%) are associated with more ROP. Until more studies have been performed, it is suggested to target SpO_2 in these babies at between 90 and 95%.

Saugstad O. *Neonatology* 2014;105:55

One of the problems is …

Achieved Versus Intended Pulse Oximeter Saturation in Infants Born Less Than 28 Weeks' Gestation: The AVIOx Study

James I. Hagadorn, Anne M. Furey, Tuyet-Hang Nghiem, Christopher H. Schmid, Dale L. Phelps, De-Ann M. Pillers and Cynthia H. Cole

Pediatrics 2006;118;1574

Data of oximeter have been recorded for 72 hours per week, for 4 weeks

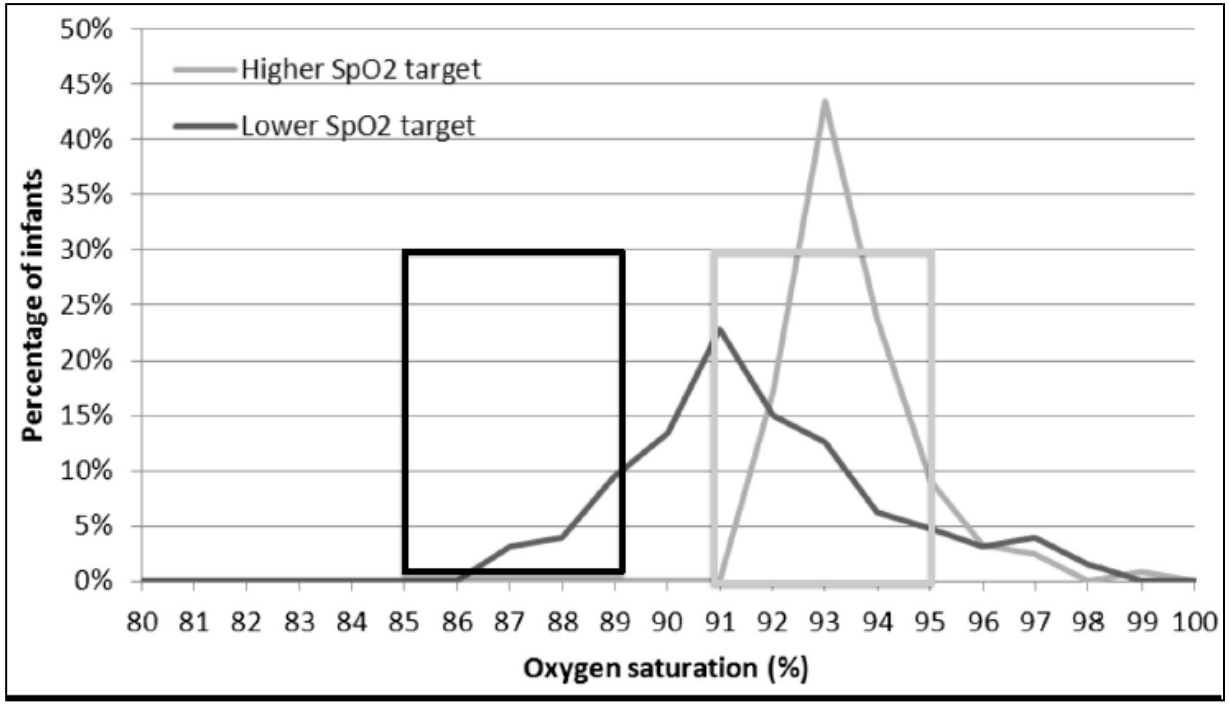
TABLE 2 Intended Spo_2 Ranges, Alarm Policy Status, Achieved Spo_2 Values, and Percentages of Time Below, Within, and Above the Intended Range, by Center

Center	Intended Spo_2 Range	Policy Regarding Tight Alarm Settings[a]	Achieved Spo_2%, SET Oximeter[b]	Percentage of Monitored Time[c]		
				Below Intended Range	Within Intended Range	Above Intended Range
A	92–96	Y	96 (94, 97)	9 (4–18)	47 (33–69)	44 (20–62)
B	90–95	N	93 (90, 96)	18 (4–31)	46 (30–52)	36 (18–65)
C	90–95	N	92 (87, 95)	36 (26–47)	44 (34–55)	20 (5–31)
D	88–95	N	95 (92, 96)	16 (12–36)	39 (26–52)	45 (14–62)
E	88–97	Y	94 (90, 96)	16 (5–30)	64 (46–75)	20 (7–49)
F	88–92	N	93 (89, 97)	20 (4–36)	19 (6–25)	61 (39–90)
G	87–94	Y	94 (91, 96)	13 (11–15)	42 (40–45)	45 (44–45)
H	92–96	Y	96 (94, 97)	18 (8–24)	55 (42–65)	27 (19–47)
I	90–96	Y	94 (92, 96)	12 (6–15)	59 (50–65)	29 (21–44)
J	85–98	N	98 (96, 100)	4 (0–6)	58 (26–75)	38 (19–73)
K	88–94	N	94 (91, 96)	17 (6–23)	40 (37–44)	43 (38–54)
L	85–94	N	93 (90, 96)	10 (3–14)	49 (27–60)	41 (28–70)
M	88–92	N	95 (92, 97)	11 (11–11)	16 (16–16)	73 (73–73)
N	83–93	Y	92 (87, 94)	11 (4–16)	51 (42–65)	38 (20–54)
All centers/patients	—	—	95 (91, 97)	16 (0–47)	48 (6–75)	36 (5–90)

- **CONCLUSION**: Success with maintaining the intended pulse oximeter saturation range varied substantially among centers, among patients within centers, and for individual patients over time. Most noncompliance was above the intended range. Methods for improving compliance and the effect of improved compliance on neonatal outcomes require additional research.

… most recently

Randomized Controlled Trial of Oxygen Saturation Targets in Very Preterm Infants: Two Year Outcomes



Many of the subjects in these studies were well outside the intended $SatO_2$ target ranges, in fact most for the lower one .

Darlow BA, et al. *J Ped* 2014; 165:30

A potential cause

Nurse:patient ratio and achievement of oxygen saturation goals in premature infants

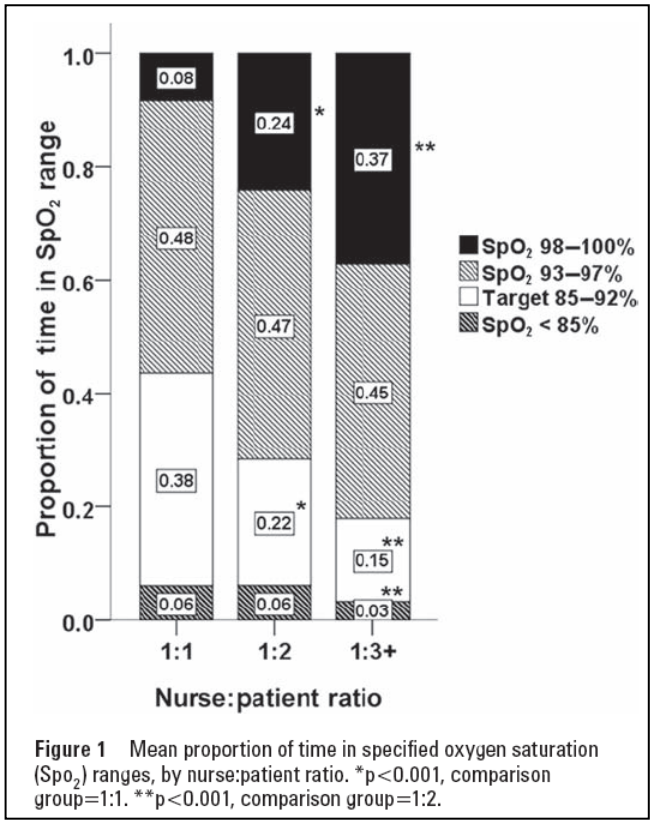


Figure 1 Mean proportion of time in specified oxygen saturation (Spo_2) ranges, by nurse:patient ratio. *p<0.001, comparison group=1:1. **p<0.001, comparison group=1:2.

- The proportion of time with SpO_2 within the target range declined from 38% to 15% with a 1:1 compared to a 1:3 or lower nurse:infant ratio.
- Fewer patients per nurse may be associated with improved achievement of oxygen saturation goals and may be an important modifiable factor influencing oxygen-related outcomes in premature newborns.

Sink DW, et al. *Arch Dis Child Fetal Neonatal Ed* 2011;96:F93

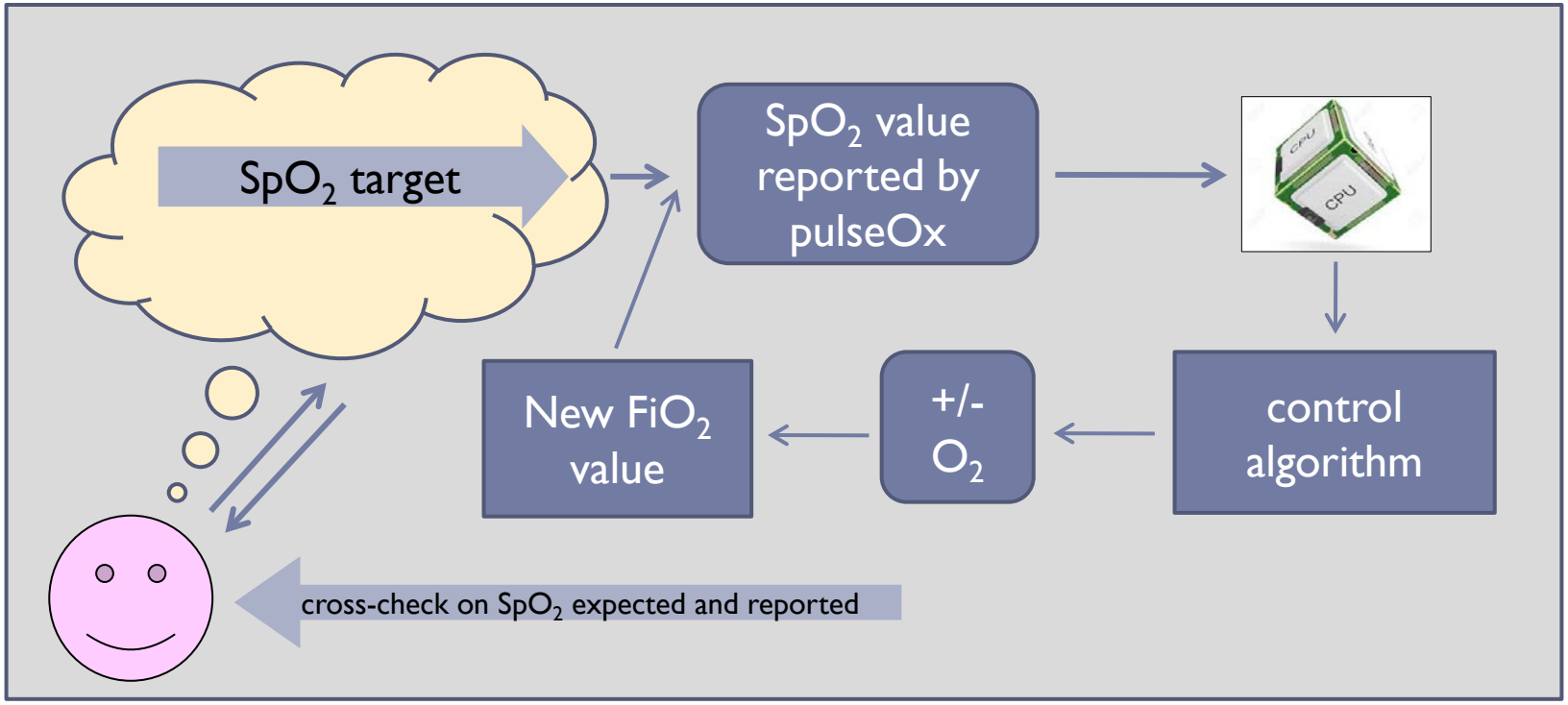
A possible solution

A closed loop FiO_2 system

- The term “closed loop” means a control system with an active feedback loop
- “closed loop FiO_2” consist of a microprocessor-based device designed to control oxygen saturation by adjusting the inspired air-oxygen mixture delivered by a mechanical blender[1]
- The first studies on closed loop control of FiO_2 have been developed since the 70s[2]

1. Morozof PE, et al. *Biomed Instrum Technol* 1992;26:117
2. Beddis IR, et al. *Arch Dis Child* 1979;54:278

Automated adjustment of O_2



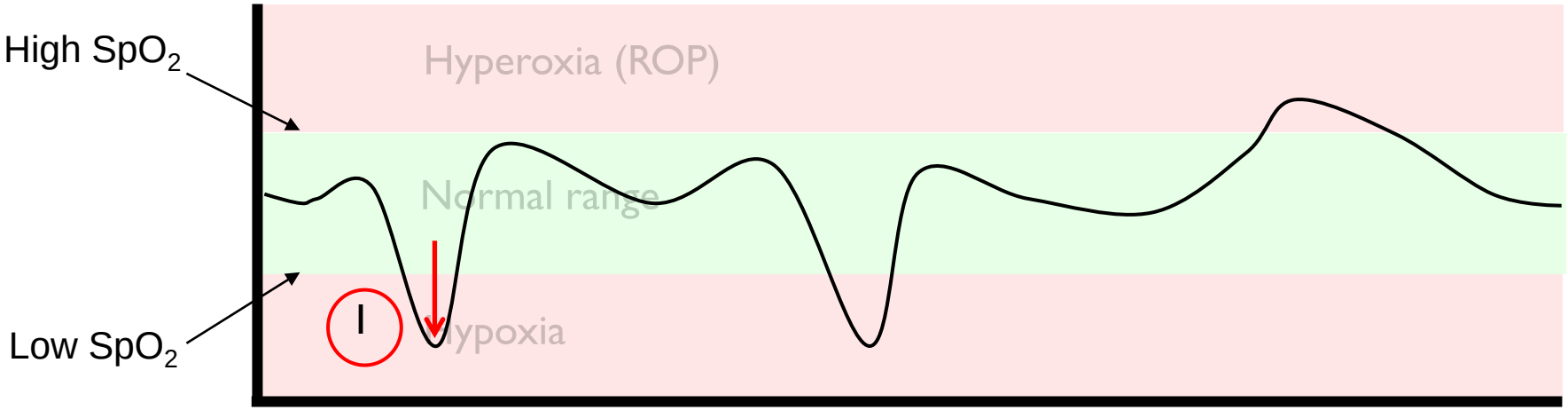
- The user sets a target SpO_2, which the controller attempts to maintain.
- FiO_2 is reduced when SpO_2 exceeds the target range or increased when SpO_2 declines below the range.
- Alarms are actuated if the patient's SpO_2 is outside predefined limits, and the delivered percentages of FiO_2 are adjusted by air-oxygen blender.

Where can we find an automatic system for the FiO_2 regulation ?

- The only "closed loop FiO_2" control systems actually commercially available (UE) is the CLiO2™ present on the AVEA mechanical ventilator (Carefusion, Yorba Linda, CA, USA).

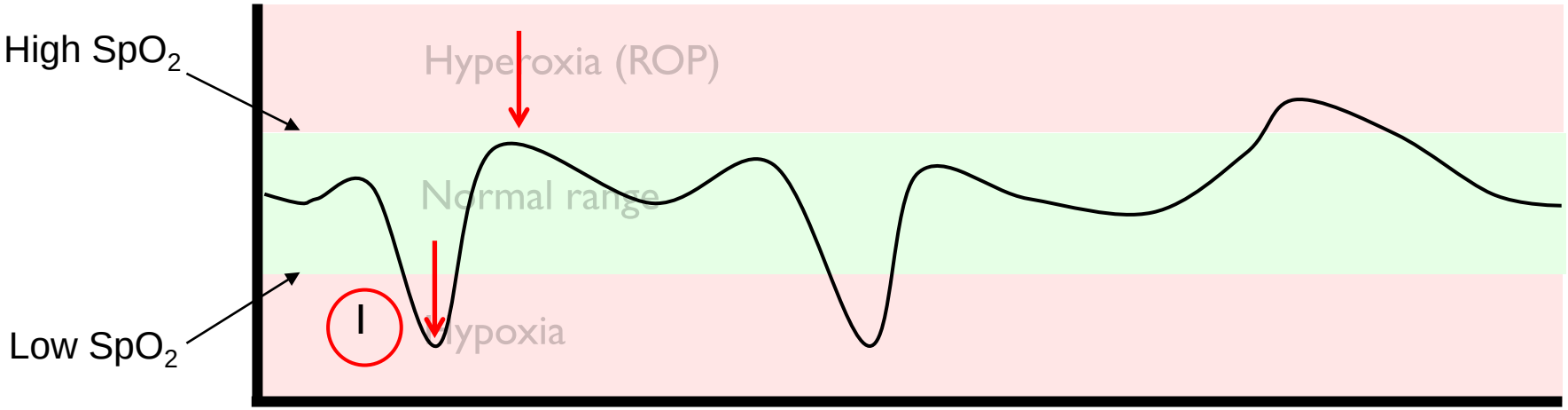
CLiO2 = **C**losed **L**oop **i**nspired **O**xygen

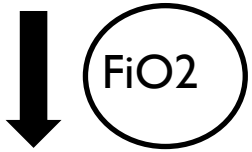
How does it work



By courtesy of Carefusion™

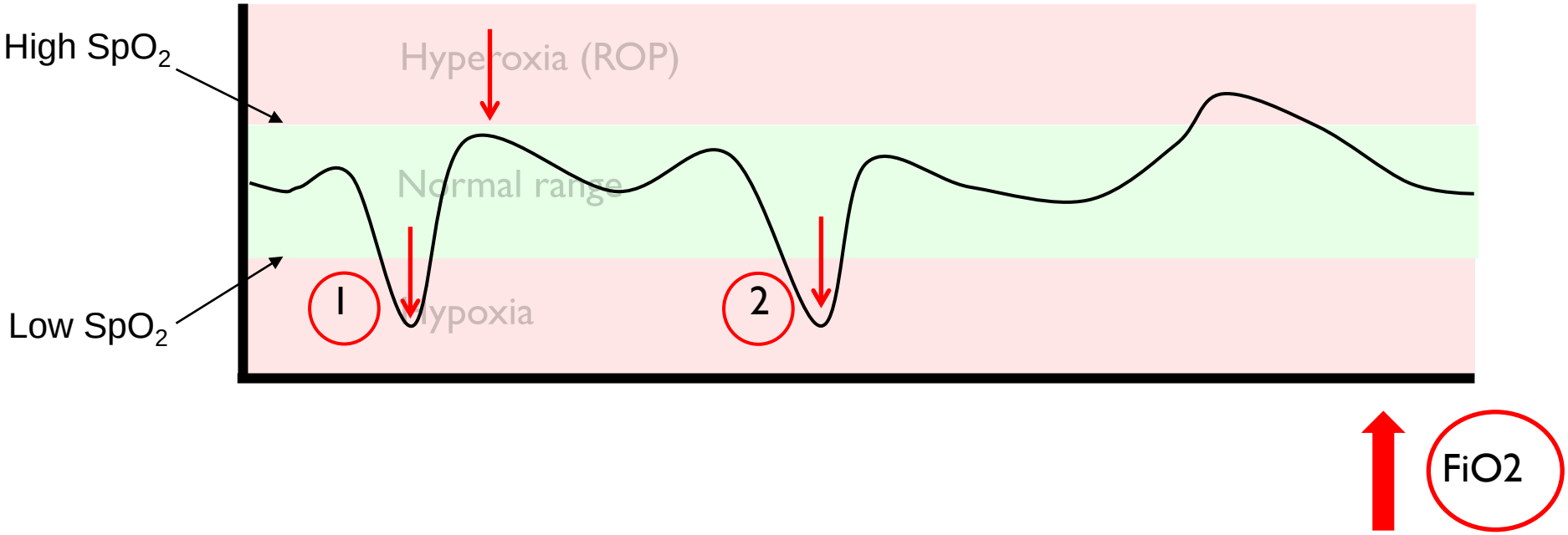
How does it work





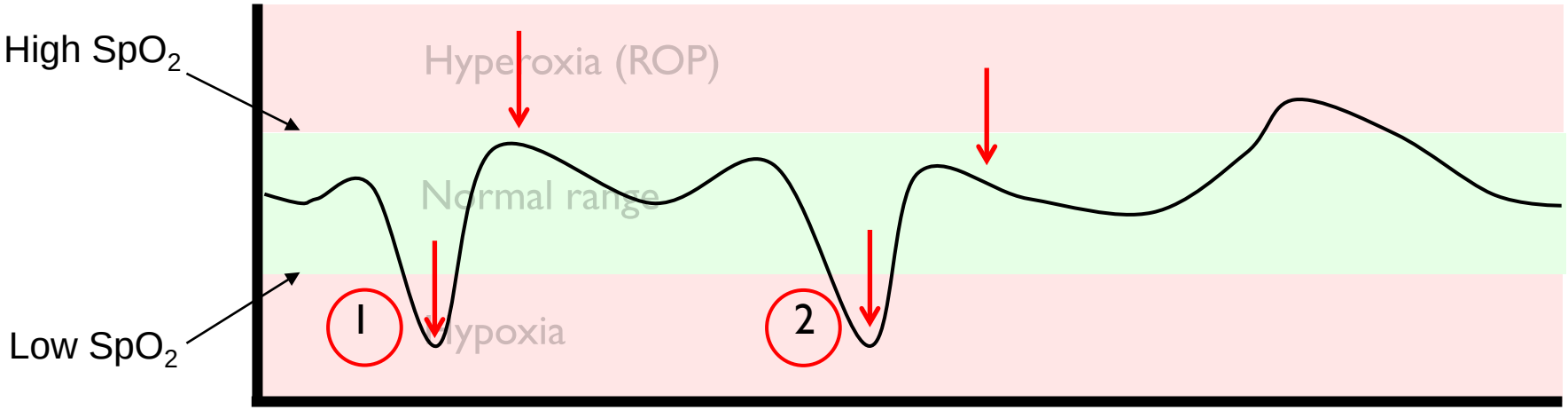
By courtesy of Carefusion™

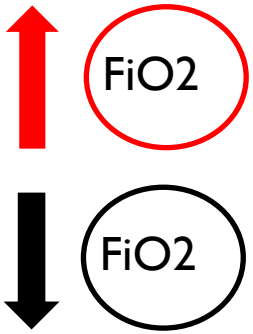
How does it work



By courtesy of Carefusion™

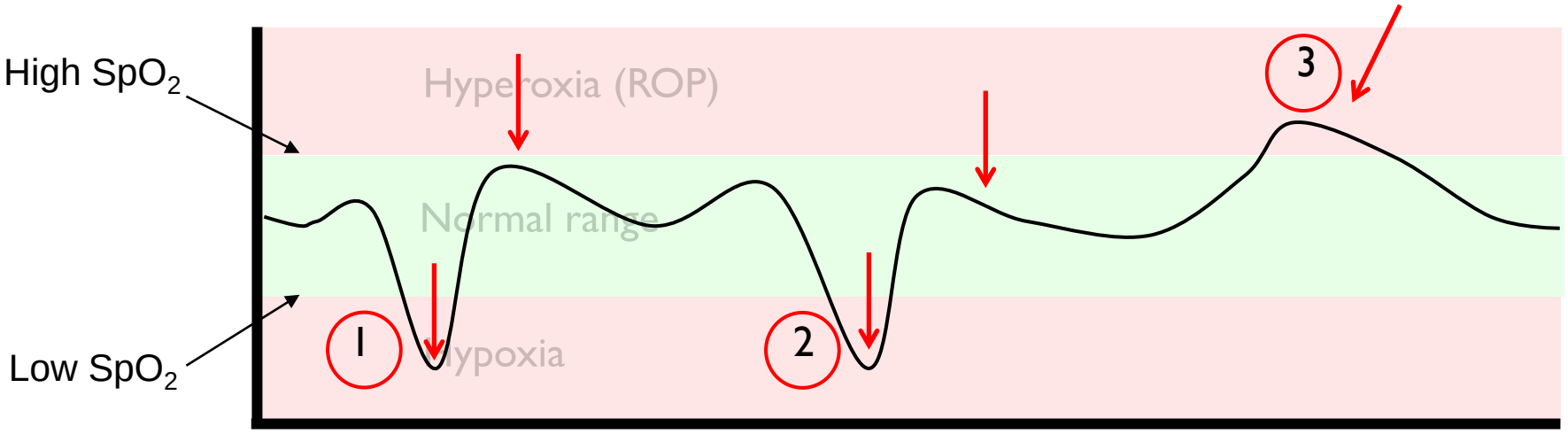
How does it work

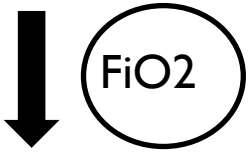




By courtesy of Carefusion™

How does it work



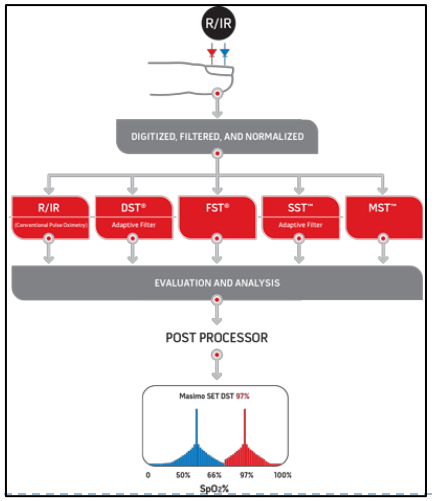


N.B.: Alarms do not "desapear" but are customizable by the user

By courtesy of Carefusion™

Pulse oximeter

- The data of arterial oxygen saturation and pulse rate are acquired, processed, and reported by Masimo Signal Extraction Technology «MasimoSET™» (Masimo Corporation, Irvine, CA, USA).
- Masimo SET's unique patented approach employs five algorithms, working in parallel, to ensure continuous, accurate SpO_2 measurement, even under the most challenging conditions.



The first "test" on ELBW

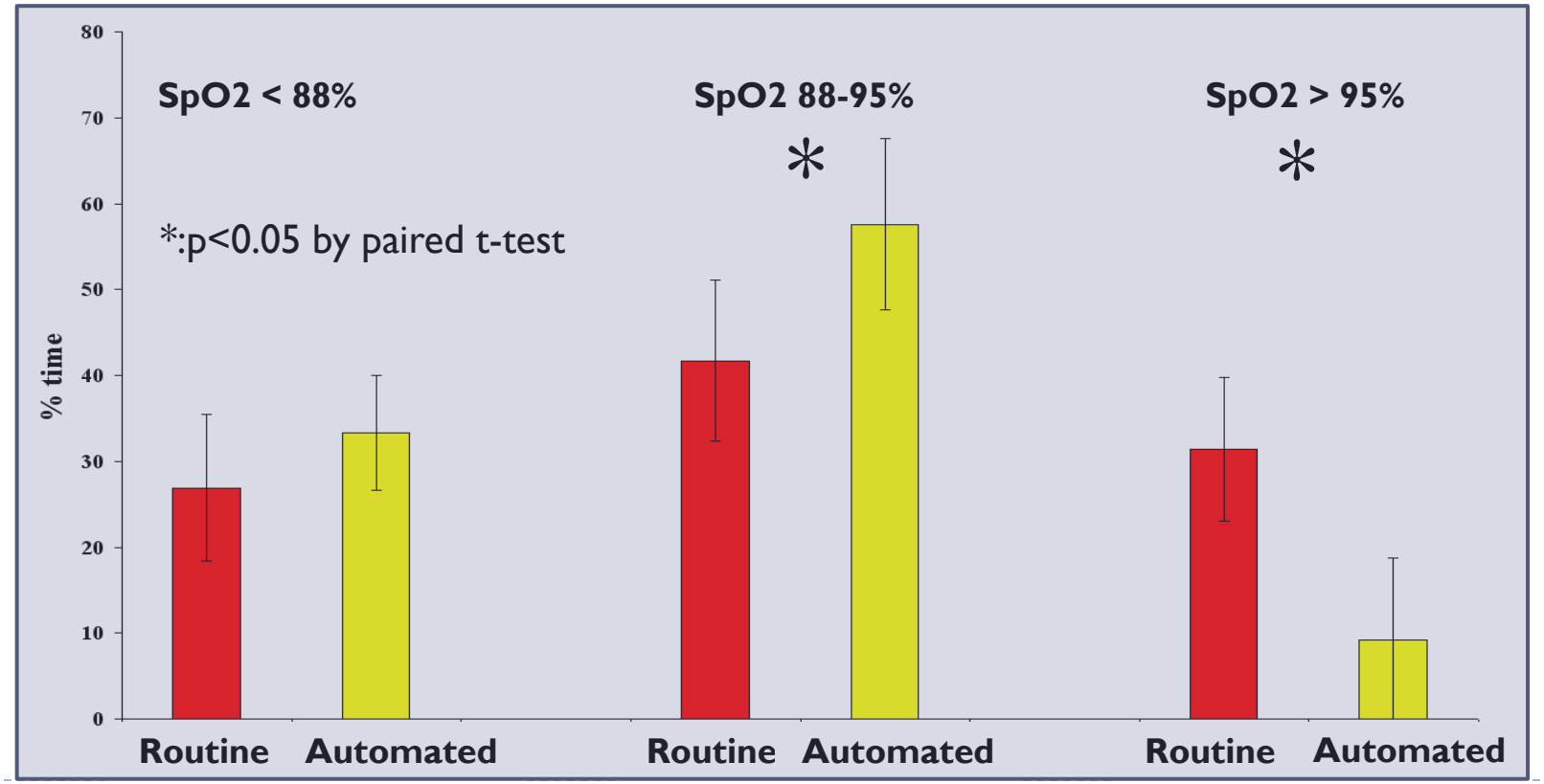
Closed-Loop Controlled Inspired Oxygen Concentration for Mechanically Ventilated Very Low Birth Weight Infants With Frequent Episodes of Hypoxemia

- Population: 14 ELBW (weight = 712 ± 142 g; GA = 25 ± 1.6 w)
- Ventilation mode: SIMV
- Study protocol: evaluation of 2 hours with automatic FiO_2 control, and 2 hours with FiO_2 adjustments by a nurse.
- CONCLUSION: Automatic FiO_2 control was at least as effective as a fully dedicated nurse in maintaining SpO_2 within the target range, and it may be more effective than a nurse working under routine condition.

Claure N, et al. *Pediatrics* 2001;107:1120

Automated Adjustment of Inspired Oxygen in Preterm Infants with Frequent Fluctuations in Oxygenation: A Pilot Clinical Trial

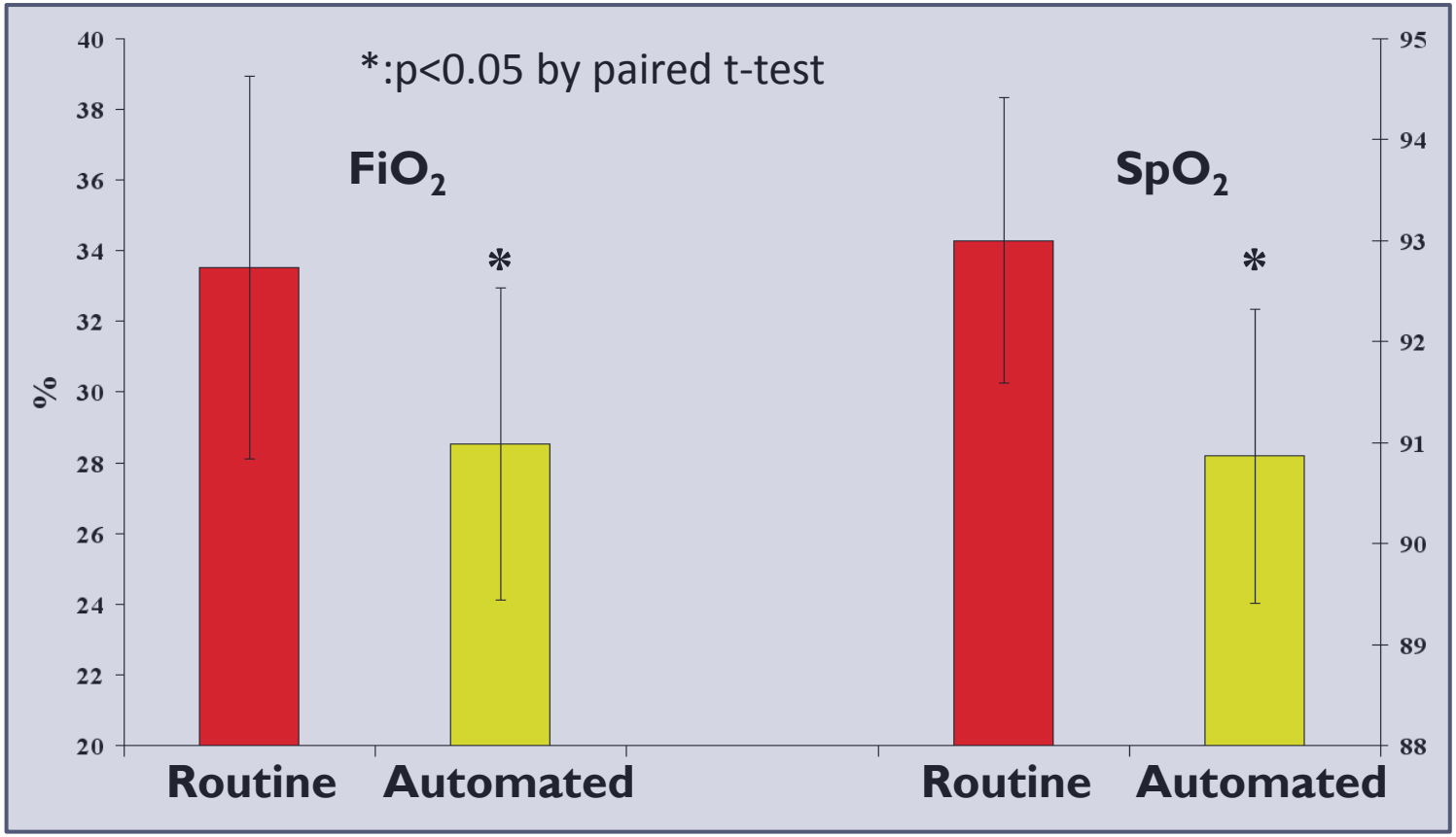
- Population: 16 ELBW (weight = 678±144 g; GA = 24.9±1.4 w)
- Age: 33±15 days with frequent hypoxia episodes
- Study protocol: 2 study period of 4 hrs each, automatic vs routinely FiO_2 control; SpO2 target range was 88-95%



Claure N, et al. *J Ped* 2009;155:640

Results

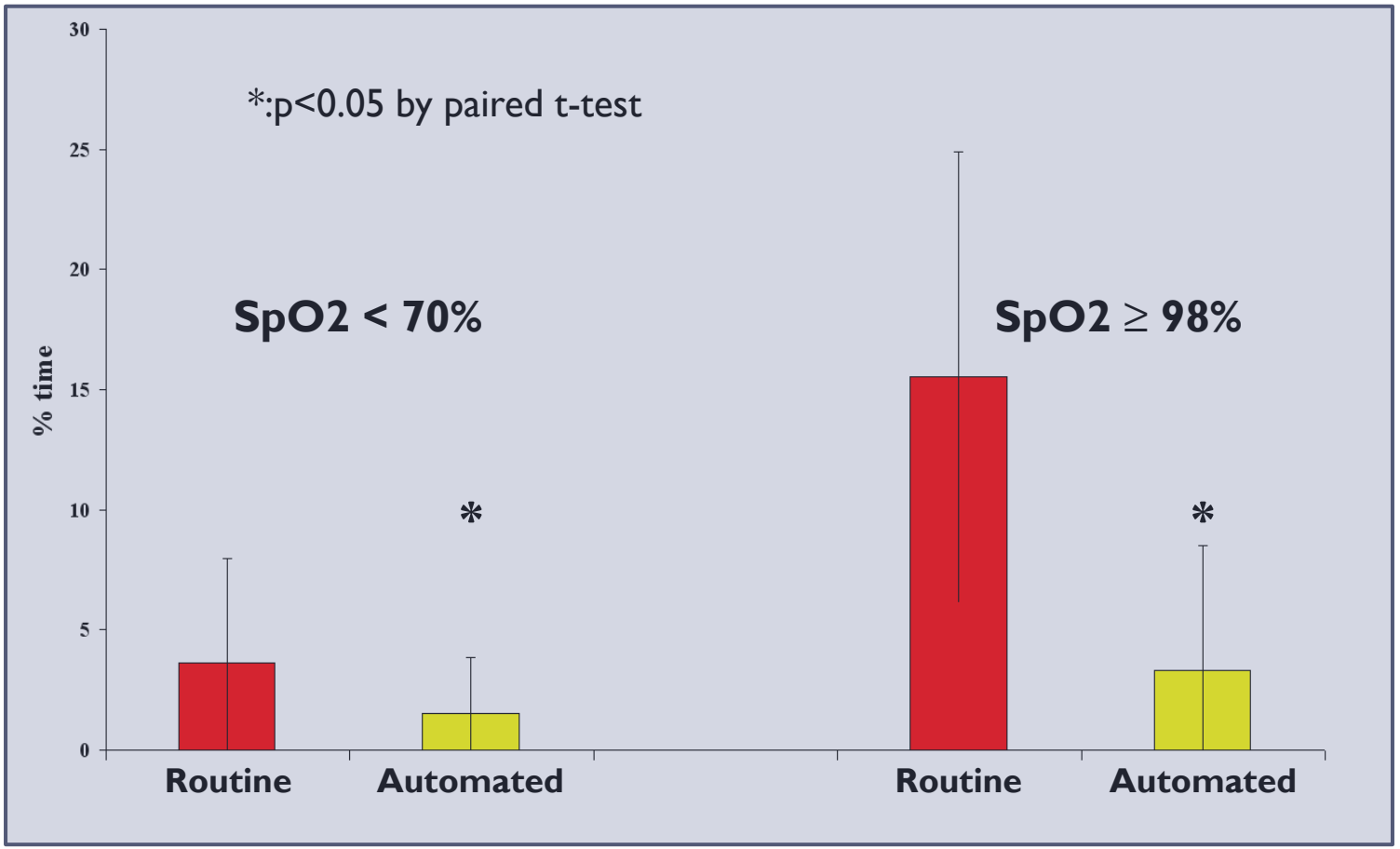
Mean SpO_2 and FiO_2 during 4 hours of observation



Claure N, et al. *J Ped* 2009;155:640

Results

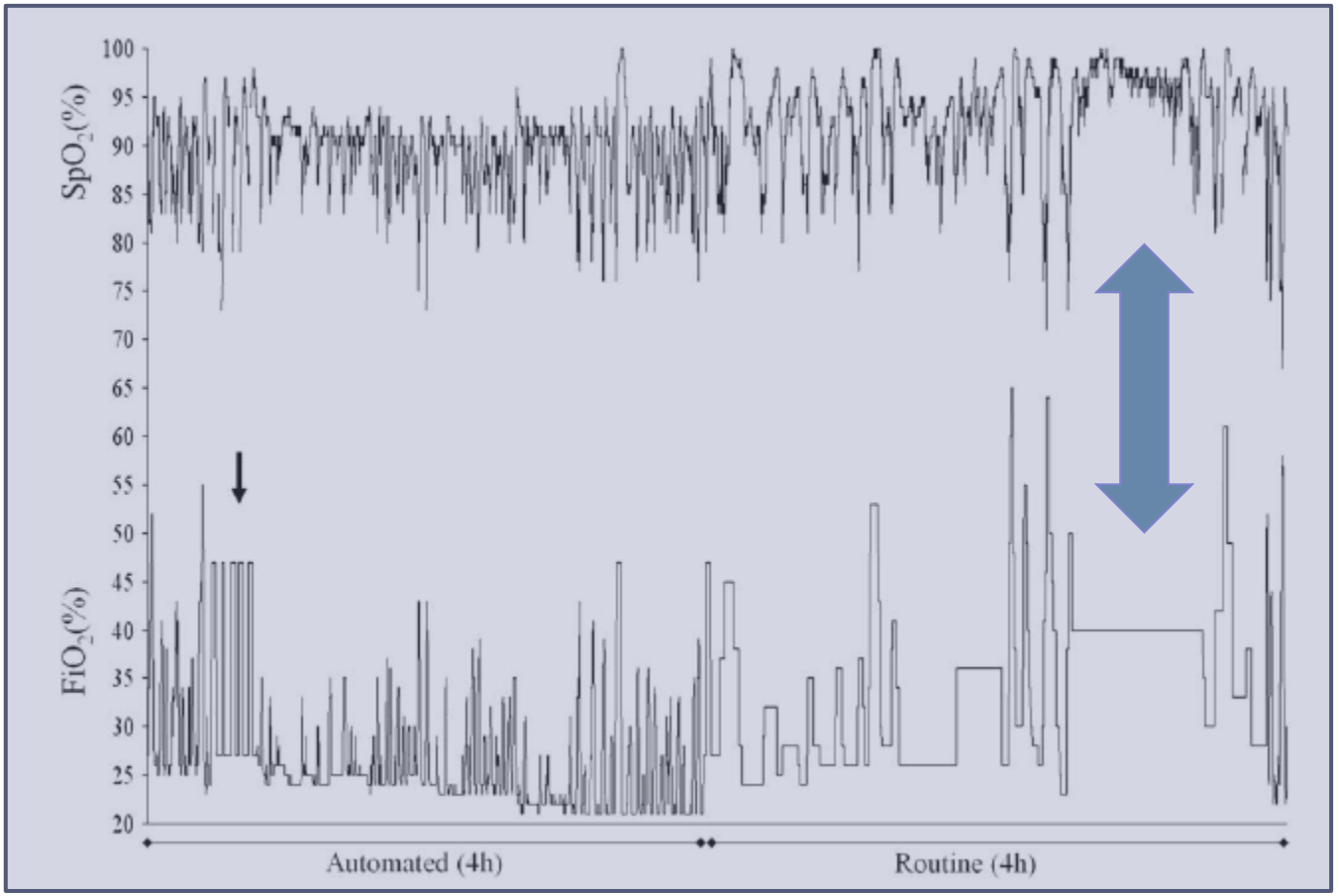
% time out of intended SpO_2 ranges



Claure N, et al. *J Ped* 2009;155:640

… and finally

Prolonged exposure to high FiO_2 %



Claure N, et al. *J Ped* 2009;155:640

Conclusions

- Oxygen is the widely used drug for the treatment of neonatal respiratory insufficiency.
- To reduce its side effects, it is required monitor Oxygen saturations carefully, maintain Sat.O_2 within the target range, and avoid Sat.O_2 fluctuation.
- Automatic FiO_2 control improves maintenance of SpO_2 within the target range; reduces the SpO_2 fluctuations and the time in severe hypoxemia or hyperoxemia in comparison with the manual control.
- Automatic FiO_2 control could allow reduce the staff workload, consenting a more efficient use of nursing time for other tasks.
- The goals of the future studies will be assess whether optimization of pulseoximetry will help to reduce the side effects of the oxygen, improving the outcome for these high risk patients.