DELFT UNIVERSITY OF TECHNOLOGY
Faculty Mechanical, Maritime
and Materials Engineering
Department of BioMedical Engineering

ERASMUS MEDICAL CENTRE
Sophia Children's Hospital

Department of Neonatology

Advisory System for Oxygen administration during Resuscitation of preterm infants

The ASOR, a clear view on oxygen saturation

T.G. Goos

Delft University of Technology, Faculty of 3mE,
Department of BioMedical Engineering
1151193
T.G.Goos@student.tudelft.nl
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Supervisors: Prof. Dr. J. Dankelman,
                Delft University of Technology, Faculty of 3mE,
                Department of BioMedical Engineering
            Dr. A. C. van der Eijk
                Delft University of Technology, Faculty of 3mE,
                Department of BioMedical Engineering
                Erasmus Medical Centre, Sophia Children's Hospital
                Department of Neonatology
            Dr. D. Rook
                Erasmus Medical Centre, Sophia Children's Hospital
                Department of Neonatology

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PREFACE

This thesis is written as the final part of my MSc Biomedical Engineering at the Delft University of Technology. The aim of this study was to improve the control of the oxygen saturation during the resuscitation of preterm infants immediately after birth. The hypothesis was that display of the trend and higher order dynamical terms in the measured oxygen saturation, and the error between the target and measured oxygen saturation, would improve the control of oxygen saturation. To this aim, the **A**dvisory **S**ystem for **O**xygen administration during the **R**esuscitation of preterm infants (ASOR) was developed which displays the trend of pulse rate, oxygen saturation and fraction of inspired oxygen, together with the oxygen saturation targets from the European Resuscitation Council guidelines. The ASOR is developed in collaboration between the Erasmus Medical Centre - Sophia Children's Hospital in Rotterdam, the Netherlands and Delft University of Technology, Delft, the Netherlands.

This thesis consists of a general introduction (chapter 1), three chapters in the form of papers, of which the first (chapter 2) is published in *Resuscitation*. The 5th chapter describes what further developments are needed to make the new ASOR monitor a success. At the end there is an overall conclusion, followed by the appendices.

The general introduction explains the clinical background and the need to improve the control of the oxygen saturation (SpO_2). The second chapter presents the results of an observational study on the current clinical performance of following the SpO_2 targets, demonstrating the scale of the problem during the resuscitation of preterm infants. Chapter three describes the development of the graphical interface of the ASOR, and the first steps that were made towards an automated controller. The resulting control scheme is able to advise the clinician on how to adjust the fraction of inspired oxygen (FiO_2), but because it is unable to monitor the ventilation parameters it is not yet suited for clinical use.

The first version of the ASOR consists of a new graphical interface, which displays all relevant data with their trends, together with the SpO_2 targets. The second version, which is under development, gives advice on when and how to adjust the FiO_2 that is given to the infant.
In the fourth chapter, the first version of the ASOR is tested in a clinical setting. During the resuscitation of preterm infants the ASOR was used, and compared to the ability to control the SpO_2 without the use of the ASOR.

In chapter five, the steps are discussed that must be taken to improve the advice given by the ASOR and ensure the correctness of the advice.

In the overall conclusion, the clinical implication of the results so far are discussed, what they mean for the development of the ASOR, and how the project should move forward.

In the appendices, background information can be found from theory on human behaviour while controlling a system, interviews conducted with the clinical staff of the Erasmus Medical Centre, where this study was conducted, risk analysis, the medical ethical application of the use of the ASOR to advice on the adjustments of the FiO_2.

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LIST OF ABBREVIATIONS

AHA	American Heart Association
ARC	Australian Resuscitation Council
ASOR	Advisory System for Oxygen administration during Resuscitation of preterm infants
BE	base excess
bmp	beats per minute
CPAP	continuous positive airway pressure
CS	caesarean section
$cSrO_2$	Cerebral regional oxygen saturation
ECR	European Resuscitation Council
ECG	electrocardiography
ELBW	extremely low birth weight
ESPR	European Society for Paediatric Research
ET	endotracheal tube
FRC	functional residual capacity
FiO_2	fraction of inspired oxygen
FTOE	Fractional tissue oxygen extraction
GA	gestational age
HUMIF	human-machine interface
HR	heart rate
ILCOR	International Liaison Committee On Resuscitation
IQR	inter quartile range
KBB	knowledge-based behaviour
MC	medical centre
NICU	neonatal intensive care unit
NIRS	near-infrared spectroscopy
NZRC	New Zealand Resuscitation Council
IQR	Inter quartile range
PaO_2	partial pressure of arterial oxygen
PEEP	positive end expiratory pressure
PID	proportional, integral, derivative
PIP	peak inspiratory pressure
RBB	rule-based behaviour
SBB	skill-based behaviour
SD	standard deviation
SpO_2	oxygen saturation measured by pulse oximetry

1. General introduction

The term 'Neonatal Resuscitation' refers to the (medical) care that newborn infants receive directly after birth. The primary task during resuscitation is aiding the infant in the transition from intra-uterine to extra-uterine life. This is done by drying the infant, checking heart rate and respiration, and if needed, intervene in order to stabilize the infant. The "Newborn life support algorithm", published as part of the resuscitation guidelines, gives a good overview of this procedure (Appendix page C: Figure 15: Newborn life support algorithm, ERC 2010)

Actually, the term 'resuscitation' creates the wrong expectation of what is done during the period right after birth. In the dictionary, 'resuscitate' is defined as, "**1** *(resuscitate the child) Revive, bring back round, save.* **2** *(resuscitate the project) revive, revivify, revitalize, restore, renew, reanimate, reinvigorate, resurrect, bring back, reintroduce, bring new life into*" [1]. What all these definitions have in common is the 'bringing back' part. As stated by C. O'Donnell, during his presentation at the European Society for Paediatric Research 2010 in Denmark, 'Resuscitation versus stabilization. The concept of transition after birth' [2], "*Many infants are born alive and do not need resuscitation*". He argues that the term stabilization would be better suited. Stabilization would be a closer resemblance to the Dutch term 'opvang', which translates as 'reception', and could be argued to be an even better term, as not all infants need actual stabilization, but all are received from their mother.

When an infant is born preterm, i.e. before 37 weeks of gestation, resuscitation plays an important role in the chances of survival [3]. Approximately 2% of all babies are born before 32 weeks of gestation [4, 5]. This group is referred to as 'very preterm infants', and often need active resuscitation because of the immaturity of their organs [3]. The first 28 days after birth a newborn infant is called a neonate, after which it is called an infant until its 1 year old [6]. Currently, prematurity ranks among the highest causes of neonatal mortality and morbidity [7]. It is ranked so high partially because preterm birth rates have been consistently rising in the last decades worldwide [8]. The reasons for preterm birth can be divided into three main categories [9]:
* Maternal or fetal indications 30 – 35%
* Spontaneous preterm labour with intact membranes 40 - 45%
* Preterm premature rupture of the membranes 25 – 30%

The rise in premature births is mainly explained by the increase of the indicated preterm birth rate [9]. Indicated preterm births are the deliveries where labour is initiated early, or the neonate is delivered by caesarean section before it is full term. The decision to deliver prematurely can be because of maternal or fetal indications. Pre-eclampsia and placenta previa remain the two main conditions related to preterm birth, while conditions such as pre-existing and gestational diabetes are claimed to be on the rise [3].

Five to ten percent of all newborn infants need active resuscitation after birth [10]. The majority of the infants that need active resuscitation are born premature. Due to the immaturity of their lungs, preterm infants often need respiratory support and supplemental oxygen therapy [11]. Unfortunately, supplemental oxygen therapy is associated with under or over exposure to oxygen. The resulting hypoxia or hyperoxia can result in e.g. damage to the eyes [12, 13], the brain [14, 15], the hearth and kidneys [16], and even death [17, 18]. Infants are born with a low oxygen saturation level (~50%), which needs to rise to ~90% [19]. Recently SpO_2 targets were introduced to guide the administration of supplemental oxygen. These targets state the acceptable oxygen saturation at specific times after birth (Table 1).

Table 1: SpO$_2$ targets at specific times after birth as stated in the ERC guidelines [20].

Minutes after birth	Target SpO$_2$
2	60%
3	70%
4	80%
5	85%
10	90%

ERC = European Resuscitation Council, SpO$_2$ = oxygen saturation.

Currently, the fraction of inspired oxygen (FiO$_2$) supplied to the infant is adjusted manually. Both the oxygen saturation measured by pulse oximetry (SpO$_2$) and the pulse rate are parameters that play an important role in the decision making whether or not to adjust the FiO$_2$. This manual control of the SpO$_2$ level is difficult and time consuming for several reasons:
- The SpO$_2$ levels change frequently and are unpredictable due to the underdevelopment of the lungs and brain [21, 22];
- Pulse oximetry is influenced by artefacts which cause a low accuracy [22, 23];
- There is no unambiguous relation determined between FiO$_2$ and SpO$_2$ [24, 25];

Predicting the trend of the SpO$_2$ level is especially difficult during the first 10 minutes after birth, when the SpO$_2$ is meant to rise, and the resuscitation is the most hectic. Misjudging the trend could result in under or overshooting the target, which exposes the infant to unwanted SpO$_2$ levels, and additional fluctuations in both FiO$_2$ and SpO$_2$.

The guidelines that state the SpO$_2$ targets for the resuscitation period are relatively new (introduced at the end of 2010), which is probably the reason why there is no published performance data on resuscitations. Performance data on controlling the SpO$_2$, available from the neonatal intensive care units (NICU's), shows that, due to earlier mentioned difficulties, only 50% of the time is spent within the intended SpO$_2$ range during routine care [26-29]. It must be noted that in the NICU there is only one nurse per 3 or 4 patients, whereas during the resuscitation of a premature infant there are at least 2 caregivers present, but they have multiple tasks to perform. During trials with a dedicated clinician adjusting the FiO$_2$ in the NICU, results improved but varied greatly; 69% (mean) [26, 27], 66% ± 14% (mean ± SD, N=14) [30], 91,0% (41.4% - 99.3%) (mean (range), N=12) [31].

At the Erasmus Medical Centre (Rotterdam, the Netherlands) the European Resuscitation Council (ERC) guidelines introduced in 2010 are used [20]. Since the guidelines only prescribe SpO$_2$ targets for the first 10 minutes after birth, the upper and lower saturation limits from their NICU are used after these initial minutes. The SpO$_2$ targets are the 25th percentile from a study by Dawson et al. [32], were the normative values of both heart rate and SpO$_2$, in 468 infants with a gestational age (GA) of 38 ± 4 weeks(SD) that did not need respiratory support, was obtained.

Although the ERC guidelines give target SpO$_2$ levels at specific times after birth, no advice is given on how these targets should be achieved. It is suggested to start the respiratory support with room air and titrate it according to the measured SpO$_2$ [20]. However, it has been shown that almost all very preterm infants need additional oxygen during resuscitation [12, 33]. (More on the initial FiO$_2$ can be found in Appendix page D: "The initial fraction of inspired oxygen during resuscitation")

The poor control of the SpO$_2$ makes research on optimal SpO$_2$ targets after birth difficult. In order to compare the result of different SpO$_2$ targets, deviation from these targets should be minimal. Also the technique of when and how the FiO$_2$ should be adjusted should be standardized, to reduce the influence of the adjustment strategy on the outcome. Such a reduction in variation will most likely improve patient care, and could help improve supplemental oxygen therapy

An automatic controller could keep SpO_2 closer to its target by adjusting the FiO_2 automatically, and continuously, thereby reducing low SpO_2 levels due to lack of oxygen, and high SpO_2 levels due to overshoot. Worldwide several groups have developed (semi-) automatic controllers for SpO_2 in a NICU setting, with promising results [30, 31, 34-37]. These controllers adjust FiO_2 (semi) automatically, when SpO_2 deviates from a target.

The first commercially available ventilator that is able to automatically adjust the FiO_2 based on SpO_2 measurement, is the Avea ventilator (with addition of the $CliO_2$ module) by CareFusion [38]. Unfortunately, this device is not suitable for the use during resuscitation. One of the reasons that the device cannot be used during resuscitation is the fact that the target SpO_2 during resuscitation depends on the time after birth, and is a gradually rising curve.

The aim of this study was to improve the control of the oxygen saturation during the resuscitation of preterm infants immediately after birth. The hypothesis was that display of the trend and higher order dynamical terms in the measured oxygen saturation, and the error between the target and measured oxygen saturation, would improve the control of oxygen saturation. To this aim, the **A**dvisory **S**ystem for **O**xygen administration during the **R**esuscitation of preterm infants (ASOR) was developed which displays the trend of pulse rate, oxygen saturation and fraction of inspired oxygen, together with the oxygen saturation targets from the European Resuscitation Council guidelines.

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2. Observing the resuscitation of very preterm infants; Are we able to follow the oxygen saturation targets?

Tom G. Goos[ab], Denise Rook[b], Anne C. van der Eijk[ab], Andre A. Kroon[b], Gerhard Pichler[c], Berndt Urlesberger[c], Jenny Dankelman[a], Irwin K.M. Reiss[b]

[a]Department of BioMedical Engineering, Faculty of Mechanical, Maritime and Materials Engineering, Delft University of Technology, Delft, The Netherlands
[b]Department of Paediatrics, Division of Neonatology, Erasmus Medical Centre - Sophia Children's Hospital, Rotterdam, The Netherlands
[c]Department of Paediatrics, Division of Neonatology, Medical University Graz, Graz, Austria

ABSTRACT

Background: Since 2010, the European Resuscitation Council (ERC) guidelines advise oxygen saturation (SpO_2) targets for the first 10 minutes of resuscitation after birth. Unfortunately, the control of SpO_2 in newborn infants is difficult.
Aim: To determine to what extent SpO_2 levels match the ERC targets during the resuscitation of very preterm infants, and how well the SpO_2 is kept within the high and low limits until the infants are transported to the NICU.
Methods: In a single-centre observational study, the SpO_2 and fraction of inspired oxygen (FiO_2) were collected during the resuscitation of very preterm infants with a gestational age (GA) $\leq$ 30 weeks.
Results: A total of 78 infants were included [median (IQR): GA $27^4/_7$ ($26-28^6/_7$) weeks, birth weight 945g (780-1140)]. During the initial 10 minutes after birth, large variations in SpO_2 were observed with deviations above the target [median (IQR)] of 4.4% SpO_2 (1.4-6.5), and below the target of 8.2% SpO_2 (2.8-16.0). After the first 10 minutes, the SpO_2 levels were respectively above and below the limit for 11% (0-27) and 8% (0-23) of the time.
Conclusion: During the resuscitation of very preterm infants, large deviations of the SpO_2 from the ERC targets are observed. During the first minutes of resuscitation the deviations were likely caused by an inability to control the SpO_2, whereas later deviations were due to weaning, pauses in respiratory support (i.e. intubation) and over exposure to oxygen. Changing the SpO_2 targets to a target range that depicts the acceptable deviation might be helpful in providing better respiratory support.

INTRODUCTION

During resuscitation of preterm infants, supplemental oxygen therapy is often used to reach and maintain adequate oxygenation. Adequate oxygenation is essential in preterm infants because both hypoxia and hyperoxia can have detrimental effects on the organs, and even fluctuations in oxygenation can be damaging.[1-3] The damage to the organs is caused by the formation of excessive oxygen free radicals.[4] The compromised anti-oxidative capacity of preterm infants and the need for a certain level of oxidative stress to initiate the adaptation from intra to extra uterine life make the control of oxygenation a delicate balance.[5]

To prevent negative outcomes due to under- or overexposure to oxygen in newborn infants, the European Resuscitation Council (ERC),[6] American Heart Association (AHA)[7] and Australian and New Zealand Resuscitation Council (ARC NZRC)[8] guidelines advise pulse oximetry oxygen saturation (SpO_2) targets for the first 10 minutes after birth. These targets are based on observational studies of healthy term and preterm infants not needing any intervention during their resuscitation.[9] To reach and maintain these SpO_2 targets, the fraction of inspired oxygen (FiO_2) is titrated manually according to the SpO_2 measurement. Unfortunately, none of the resuscitation guidelines specify how the FiO_2 should be titrated to make sure SpO_2 targets are reached.

Literature shows that manual control of the SpO_2 is difficult, reporting time spent outside the target range of approximately 50% in neonatal intensive care units (NICU).[10-13] Although the status of the infants and the tasks of the physicians in NICUs differ from that during resuscitations immediately after birth, it is likely that during delivery room resuscitation it is difficult for clinicians to keep SpO_2 within the recommended target range. It is unknown to what extent the SpO_2 targets are achieved. Therefore, the aim of this study was to determine to what extent SpO_2 levels matched ERC targets during the resuscitation immediately after birth of very preterm infants.

MATERIALS AND METHODS

An observational study was performed at the Erasmus Medical Centre - Sophia Children's Hospital, Rotterdam, the Netherlands, a level-III-c NICU with 33 beds.[14] The medical ethics committee of the Erasmus Medical Centre approved this study (ASM/hl/135583), and decided that informed consent was not needed because no interventions were imposed and no personal data was processed. Because of the observational nature of this study, there was no possibility to determine a sample size.

Subjects

Patients born with a GA ≤ 30 weeks in the study centre were eligible for inclusion in this study. Congenital or chromosomal defects were exclusion criteria.

Local resuscitation protocol

The ERC guidelines were introduced 7 months prior to the start of this study. They were discussed amongst the staff prior to being adapted as the local resuscitation protocol, and are part of the education of resident physicians. A reminder of the SpO_2 targets was available in all resuscitation areas, together with a Dutch translation of the ERC 'Newborn life support algorithm'.[15]

According to the local protocol, preterm infants were transferred to the resuscitation unit immediately after delivery, where at least 2 clinicians start to stabilise the infant. Resuscitation of infants < 26 weeks GA is performed by a neonatologist or neonatal fellow. Measures were taken to prevent heat loss. Respiratory support was given, primarily with a T-piece resuscitator (Neopuff, Fisher & Paykel Healthcare, Auckland, New Zealand). A flow-inflating bag with pressure monitoring (Jackson Reese modification T-piece breathing system, Intersurgical, Wokingham, UK) was also available and could be used according to the physician's preferences. Contrary to the advice of the ERC guidelines to start all resuscitations with room air, local protocol advises to start resuscitation of infants with a GA ≤ 28 weeks with an FiO_2 of 0.30 (based on publications by Escrig et al., Vento et al. and Saugstad et al.[16-18]). Furthermore, FiO_2 should not be adjusted before an SpO_2 measurement is obtained, unless the heart rate, obtained from auscultation, drops below 100 beats per minute (bpm).[6] A pulse oximeter sensor (Nellcor OxiMax Max-N, Covidien, CO, USA) was placed on the right hand or wrist to measure preductal SpO_2.[19]

During the first 10 minutes after birth, the SpO_2 targets from the ERC guidelines were advised, i.e. 60%, 70%, 80%, 85%, and 90% at 2, 3, 4, 5, and 10 minutes after birth, respectively (Figure 1A). From the 10th minute onwards, the target range of the study centre's NICU were prescribed (85-93% SpO_2).[20] When respiration was absent or insufficient, ventilation was initiated with sustained inflations, i.e. 5 inflations of 3 seconds, after which respiratory support could be optimised by adjusting the positive end expiratory pressure (PEEP) and/or peak inspiratory pressure (PIP) (initially set to 5 and 20 cmH_2O respectively). When respiration of the infants remained insufficient or if the infants remained hypoxic, endotracheal intubation was performed.

Outcome parameters

The primary outcome was the deviation of SpO_2 from a trend line drawn through the ERC targets and, after the 10th minute, the target range for SpO_2. Deviation from the target was assessed by the time spent above and below the target and by calculating the average absolute deviation per infant.

$$A\textit{verage absolute deviation} = \left(\frac{\sum_{measurements\ outside\ range} |\text{target } SpO_2 - \text{measured } SpO_2|}{number\ of\ measurements\ outside\ range} \right)$$ (1)

The deviation above the target was corrected for those moments when the SpO_2 was above the target while the infant was on room air (FiO_2 0.21). The secondary outcomes were the time to obtain SpO_2 measurement, total resuscitation time, administered FiO_2, and number of intubation attempts.

Data collection

Measurements were obtained from the pulse oximeter (Nellcor N-600x, Covidien, CO, USA) and recorded with a frequency of 0.5 Hz from the first measurement until the infant was disconnected for transfer to the transport incubator. The FiO_2 was obtained (1 Hz) through an oxygen monitor (MX300, Teledyne Technologies, City of Industry, USA) that was connected to an oxygen sensor (M-15 STD, IT Dr. Gambert GmbH, Wismar, Germany) in the blender's bleed port (Bird Ultrablender, Cardinal Health, Dublin, USA) . The time of birth was defined as the moment at which the APGAR timer was started. When the APGAR timer was not started, a time of 30 seconds prior to the infant being placed on the resuscitation unit was taken as the time of birth. In the 67 infants where the APGAR timer was started at birth it took a median (IQR) 30 (21-36) seconds for infants to be placed on the resuscitation unit. Data acquisition was performed on dedicated research computers, continuously running software specially written for this study (programmed in Labview 2011, National Instruments, Austin, USA).

RESULTS

Seventy-eight infants were included during an 8-month period (see Table 2 for patient characteristics). The results are presented as median (IQR) unless stated otherwise. Of the 142 eligible infants, 42 were excluded [GA $27^3/_7$ ($25^4/_7$-$28^4/_7$) weeks, birth weight 870g (763-1050)] because they were included in one of two (interventional) studies that conflicted with the initial adjustment of the FiO_2.[21] The data of 21 patients [GA $27^4/_7$ ($26^3/_7$-$28^4/_7$) weeks, birth weight 955g (828-1186)] could not be used for analysis due to failure of the data acquisition. The failures of the data acquisition were purely technical, related to connections between the medical devices, the software, or the computer failing, which resulted in the data not being recorded. One infant was retrospectively excluded due to a congenital defect. There was a failure to start the APGAR timer in 11 cases (14%).

Table 2: Patient characteristics

Patients (N)	male: female	41 : 37
GA (weeks)		$27^4/_7$ (26-$28^6/_7$)
GA ≤28 weeks (N)		51
Birth weight (g)		945 (780-1140)
Mode of delivery (N)	vaginal : CS	33 : 45
Reason for elected preterm delivery	maternal : fetal	11 : 31
Received full course of corticosteroids (N)		43
Cord blood (arterial)	pH	7.31 (7.05-7.48)
	BE (mmol/l)	-2.4 (-4.0--1.4)
APGAR score at 5 min after birth		8 (7-9)

Data represented as number (N) or median (IQR). CS = caesarean section, GA = gestational age.

Deviation from the SpO_2 targets

During the first 10 minutes after birth, the time spent above [44% (12-66)] and below [51% (27-82)] the intended SpO_2 target was similarly distributed (Table 3), with a median deviation from the target of 8.2% SpO_2 (2.8-16.0). After the first 10 minutes, until the infant left the resuscitation area, 32% (14-46) of the time was spent outside of the NICU limits. The measured SpO_2 is plotted together with the ERC targets for SpO_2 and the NICU limits in Figure 1A. Figure 1 also shows the measured pulse rate (Figure 1B), administered FiO_2 (Figure 1C), and the number of infants that were on the resuscitation unit at that specific time after birth and contributed data (Figure 1D) (a more detailed view of the SpO_2 during the first 10 minutes of the resuscitations can be seen in Figure 3). There were 21 large drops in the SpO_2 (<60%), which were all the result of intubation attempts. In 41 infants (53%), the SpO_2 was at some point above the target, while the FiO_2 was 0.21, for which the deviation was corrected. During the first 10 minutes after birth, this correction occurred for a total of 9% of the time (67 min) and for 3% of the time (64 min) during the remainder of the resuscitations. Only 6 infants (8%) remained inside the limits after the first 10 minutes.
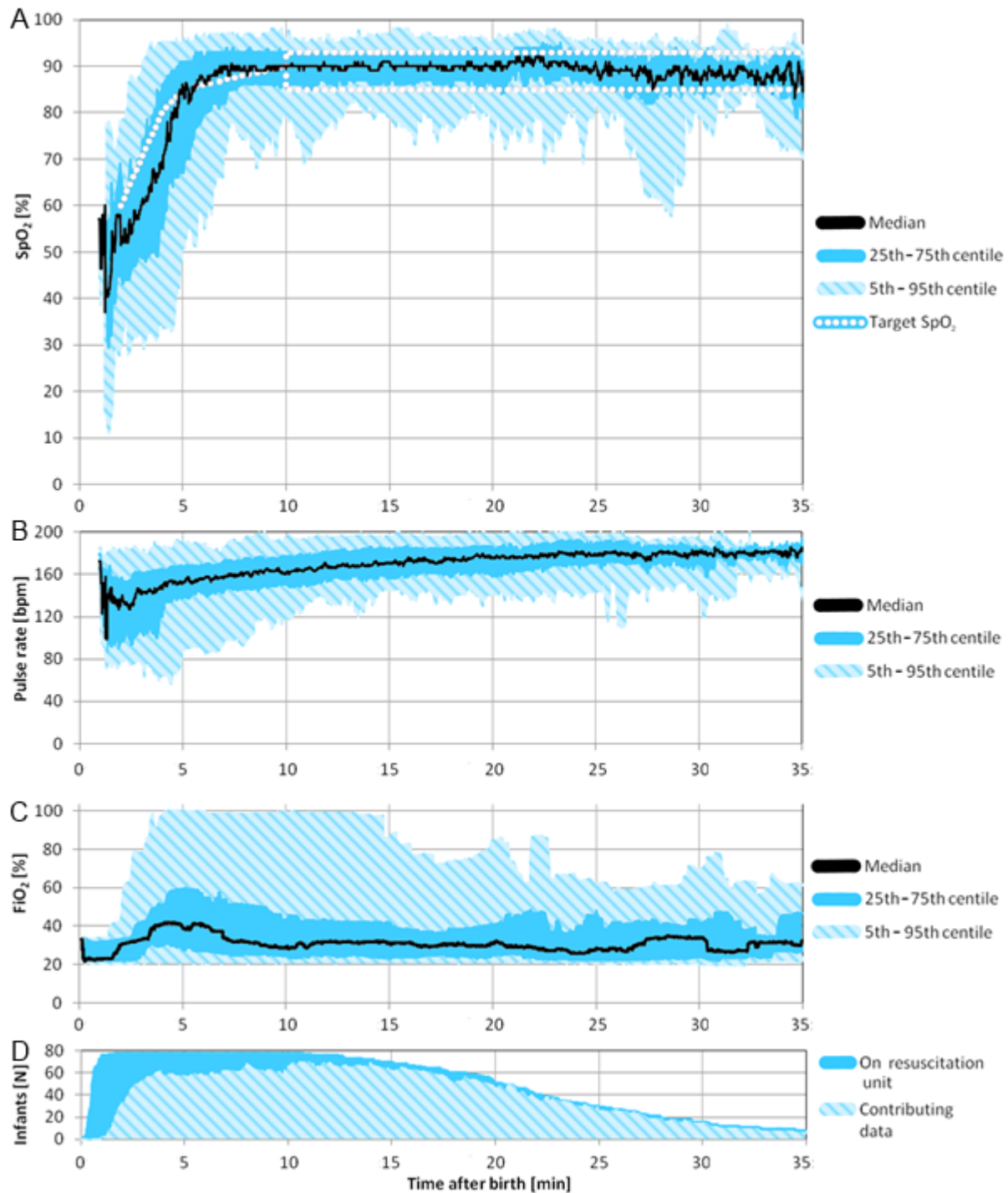
Figure 1: Measured oxygen saturation (SpO₂) and fraction of inspired oxygen (FiO₂) during the resuscitation of preterm infants (N=78).
(A) Median, 5th, 25th, 75th and 95th percentile of the SpO₂ measured during resuscitation, plotted together with the European Resuscitation Council (ERC), and high and low SpO₂ targets, as used at the Erasmus Medical Centre (Rotterdam, the Netherlands). (B) Median, 5th, 25th, 75th and 95th percentile of the measured pulse rate. (C) Median, 5th, 25th, 75th and 95th percentile of the FiO₂ administered during the resuscitation. (D) Number of infants that were on the resuscitation unit at specific times after birth, and number of infants that were contributing to the data set.

Table 3: Primary results

SpO$_2$ deviation during the first 10 minutes after birth	
Time above ERC target (%)	44 (12-66)
Time below ERC target (%)	51 (27-82)
Average deviation above ECR target (% SpO$_2$)	4.4 (1.4-6.5)
Average deviation below ECR target (% SpO$_2$)	8.2 (2.8-16.0)
Average deviation (% SpO$_2$)	7.8 (5.8-12.5)
SpO$_2$ deviation after the first 10 minutes after birth	
Time above NICU limit (%)	11 (0-27)
Time below NICU limit (%)	8 (0-23)
Time outside NICU limit (%)	32 (14-46)
Average deviation above NICU limit (% SpO$_2$)	1.7 (0.3-2.5)
Average deviation below NICU limit (% SpO$_2$)	2.0 (0.0-5.1)
Average deviation (% SpO$_2$)	2.6 (1.3-4.5)
SpO$_2$ deviation during the entire resuscitation	
Total time above target (%)	25 (11-40)
Total time below target (%)	26 (14-39)
Average deviation above target (% SpO$_2$)	3.5 (2.4-5.4)
Average deviation below target (% SpO$_2$)	7.3 (3.2-13.3)
Average deviation (% SpO$_2$)	6.6 (4.6-9.6)
FiO$_2$ adjustments	
Number of adjustments (N)	7 (3-10)
Average FiO$_2$ (%)	33.5 (26.8-44.9)
Min FiO$_2$ (%)	21.0 (20.5-22.4)
Max FiO$_2$ (%)	59.0 (36.9-99.3)
FiO$_2$ at the end of resuscitation (%)	26.2 (22.2-33.0)

Data represented as median (IQR). ERC = European Resuscitation Council, FiO$_2$ = fraction of inspired oxygen, NICU = neonatal intensive care unit, SpO$_2$ = oxygen saturation.

Secondary outcomes

The infants spent 22:24 (19:08-28:01) minutes on the resuscitation unit. The interval between the moment that the infant was placed on the resuscitation unit and the first SpO$_2$ measurement was 1:29 (1:15-2:16) minutes. In 67 resuscitations (86%), the SpO$_2$ sensor was positioned on the extremity of the infant before the connector of the sensor was plugged into the monitor, which is the quickest method for obtaining an accurate measurement.[22] At the moment of the first ERC target (2 minutes after birth), the measurements from 33 infants were obtained (42%).

For infants with GA ≤ 28 weeks, the initial FiO$_2$ was 0.30 in 29 cases (57%), in one case it was set to 0.40, and in the other cases room air was used. In one case the FiO$_2$ was corrected to 0.30 almost immediately. Two infants with a GA > 28 weeks (8%) received an initial FiO$_2$ of 0.30. The FiO$_2$ was increased before there was an SpO$_2$ measurement in 16 cases. In 9 of these 16 cases (56%), we could confirm that it was because of a low heart rate. When leaving the resuscitation area, the median FiO$_2$ of all infants was 26.2% (22.2-33.0). When an infant needed to be intubated (N=28, 36%), 2 (1-2) attempts were needed to do so successfully. Thirty-two infants (41%) left the resuscitation area with a nasal cannula, the others with mask ventilation (N=18, 23%).
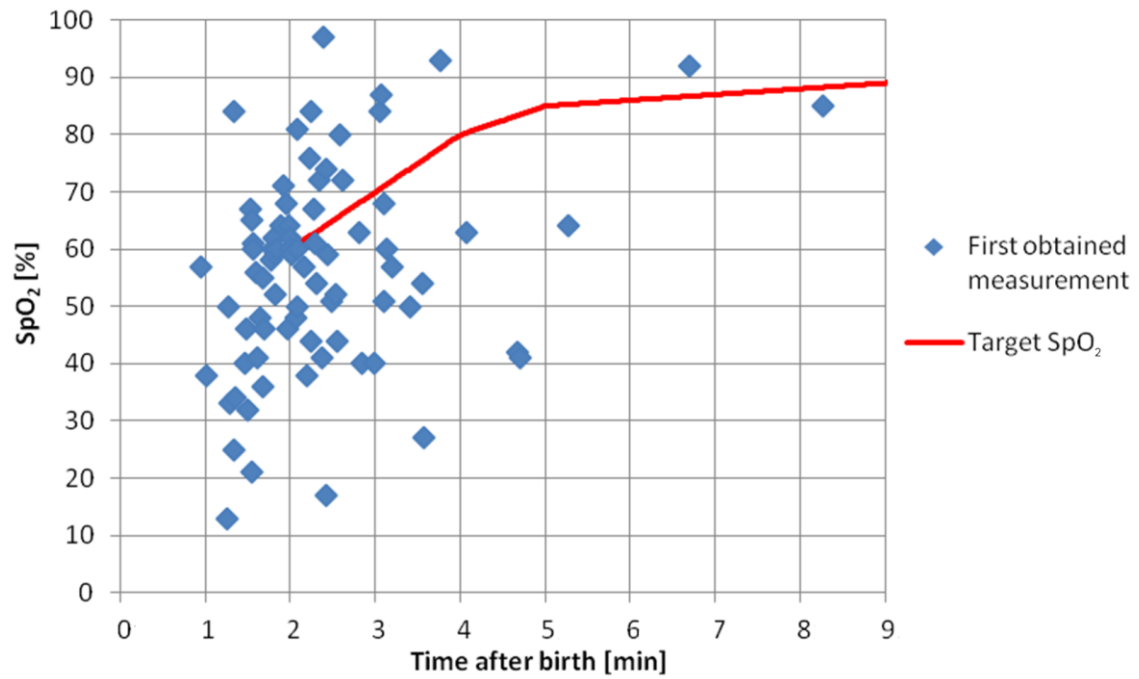
Figure 2: First oxygen saturation measurement (SpO$_2$) of the resuscitated infants (N=78) at the time after birth the SpO$_2$ measurement was obtained.

DISCUSSION

This study determined to what extent SpO_2 levels matched the ERC targets during the resuscitation of preterm infants in daily practice. While the median of the observed infants followed the ERC targets quite nicely, it did deviate below the targets during the first 5 minutes after birth. Overall the variation in the SpO_2 was large. The average deviation from the targets was 6.6% SpO_2 (4.6-9.6), whereas the deviation more than doubled in the worst cases (95th centile 19.3% SpO_2) (Figure 1A and Figure 1).

There are several possible explanations for the large deviations during the first few minutes after birth. First, in some infants, the first SpO_2 measurement took longer to obtain (Fig. 2), which is most likely caused by poor perfusion, or problems with sensor placement.[23, 24] A longer time to obtain an SpO_2 measurement will increase the time until control over the SpO_2 is achieved, because the FiO_2 is not adjusted without an SpO_2 measurement unless the heart rate is below 100 bpm. Such a delay could cause a further deviation from the SpO_2 targets. Second, during the initial phase of resuscitation, ventilation of preterm infants is hampered by lung immaturity, resulting in inappropriate aeration of the lung, i.e. establishing functional residual capacity.[25] Other explanations for suboptimal ventilation could be mask leaks or airway obstructions.[26, 27]

The median of the administered FiO_2 rose sharply on two occasions, before 2 and shortly after 3 minutes after birth. The first rise is likely due to the initial assessment of the infant, the second rise because the SpO_2 measurement became available. Between 4 and 5 minutes after birth the median of the SpO_2 rose to follow the targets more closely and a reduction of the variation in pulse rate was observed. These combined results of respiratory support, improved lung recruitment and perfusion, indicates that in most infants control adequate respiratory support was obtained at this point.[27]

After the first 10 minutes, 32% (14-46) of the time was spent outside the SpO_2 limits. On average 36% (31-47) of the infants were outside the SpO_2 limits at any given time. Thus, even with adequate respiratory support, remaining between the high and low SpO_2 levels was challenging. Instability in the oxygenation was caused by, for example, a temporary halt in the respiratory support (i.e., tube placement or suctioning) but can also be caused by incomplete adaptation.[28] The time spent above the intended range was the result of the administration of a too high FiO_2 and could have been avoided by reducing the FiO_2. However, determining by how much the FiO_2 should be reduced is one of the major challenges in controlling the SpO_2, and the fear of low SpO_2 values might deter physicians from making rapid adjustments.

The APGAR time was not started in 14% of the resuscitations, indicating that the staff is not always fully focused on starting the timer. The not starting of the timer will make the following of the SpO_2 targets more difficult, because an exact time after birth is not readily available to the physicians. Compliance with the local protocol to start resuscitation of infants ≤28 weeks GA with a FiO_2 of 30% was low (57%).

The ERC guidelines prescribe single value SpO_2 targets, while the AHA and ARC guidelines advise a narrow SpO_2 target range.[7, 8] A target range provides physicians with information on what is considered to be an acceptable deviation, and could actually reduce the observed variation. A group of experts on the resuscitation of preterm infants has suggested using the 10th and 50th centile of the study of Dawson et al.[9] (the same study as which the current guidelines are based on), as the SpO_2 target range, which is a significantly lower low target than the other SpO_2 targets (Figure 3).[29]

When our results are compared to the observations of Dawson et al. of preterm infants (<32 weeks GA, N=39) who did not require medical intervention after birth, it seems likely that most infants were in a safe range with their SpO_2 values (Figure 3).[9] However during the first 6 minutes after birth more than 25% of the observed infants had SpO_2 values that were below the 10th centile. Whether single value SpO_2 targets or target ranges result in more accurate control of the SpO_2 during routine clinical resuscitations needs to be determined. Furthermore, it remains unknown which SpO_2 targets, or target range provide the best compromise between exposure to oxygen and avoiding hypoxia. To determine the effects of the SpO_2 targets, long-term (follow up) studies are needed. However, to study the effects of different SpO_2 targets, current clinical practice must be able to control the SpO_2 adequately, and follow the targets with as little deviation as possible.
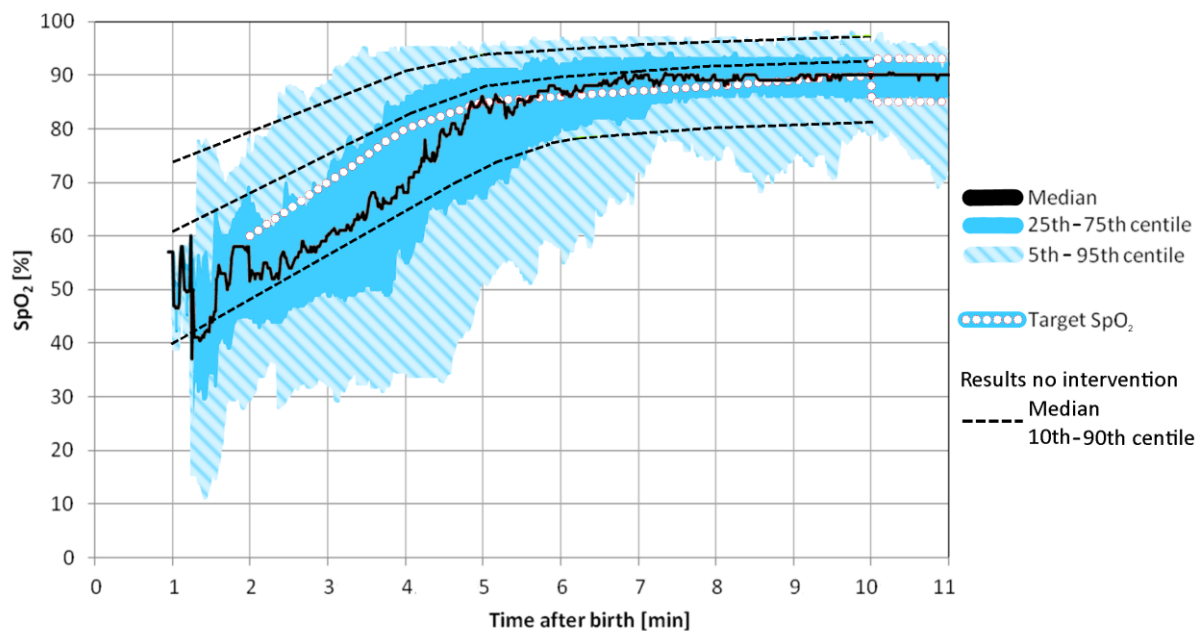
Figure 3: Comparison of the median, 5th, 25th, 75th and 95th percentile of the oxygen saturation (SpO_2) measured during the first 10 minutes of resuscitation of preterm infants (N=78), to the median, 10th and 90th centile of preterm infants (<32 weeks gestational age, N=32) that did not receive any medical intervention after birth as observed by Dawson et al.[9]
The number of infants on the resuscitation unit and the number that was contributing data can be found in fig. 1D.

There are a few drawbacks to this study. Compliance with local protocol to start resuscitation of infants >28weeks GA was low (57%). It was performed in a single centre and it is unclear to what extent the results are representative of other centres. Patients stayed within the NICU limits 68% (54-86) of the time, which is similar to the results of studies with dedicated clinicians adjusting the FiO_2 in the NICU.[10, 11, 30]

Other new technological developments may help improve SpO_2 control. Providing the physician with constant feedback on deviations from the target SpO_2 could improve performance during resuscitation. With the improvement of pulse oximeters, which can provide measurements even when the infant has poor perfusion, comes a need to better understand how perfusion influences tissue oxygenation and how it changes after birth. But it will remain important to not overload the physician with information and devices to look at, as this takes the focus away from the infant. Closed loop SpO_2 control is available for use in a NICU setting (CliO$_2$, CareFusion, San Diego, USA).[31] Similar technology might be beneficial during resuscitation, as it would keep the physician free to focus on the infant, instead of fine-tuning the equipment.

CONCLUSIONS

In conclusion, in our institution, the SpO_2 targets were not always followed accurately during the initial minutes after birth. At the start of resuscitation, deviations were most likely caused by an inability to control the SpO_2, i.e., no lung aeration and/or no initial SpO_2 measurement, resulting in low SpO_2 values. Whereas after the infants were stabilised, the deviations were due to weaning, pauses in respiratory support (i.e., intubation), and/or overexposure to oxygen. The ERC advise acceptable SpO_2 targets, which leaves it to the individual physician to decide how much deviation is acceptable. By changing the SpO_2 targets to a target range that depicts the acceptable deviation the targets could aid physicians in providing better respiratory support, and possibly reduce variation.

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3. Development of an Advisory System for Oxygen administration during the Resuscitation of preterm infants (ASOR)

ABSTRACT

AIM: To develop a device that will improve the control of the oxygen saturation measured by pulse oximetry (SpO_2) and reduces the deviation from the oxygen saturation targets, during the resuscitation of preterm infants after birth.

METHOD: The ASOR (**A**dvisory **S**ystem for **O**xygen administration during the **R**esuscitation of preterm infants) was developed, combining the measured SpO_2, pulse rate and fraction of inspired oxygen (FiO_2) with the SpO_2 targets, and displays their trends on a single screen. The possibility of an advisory system that recommends FiO_2 adjustments to the physician was explored.

RESULT: The first version of the ASOR consist of software that reads out existing medical devices and a graphical user interface that displays all relevant information to the physician. The display shows the measurements of the last 10 minutes in a single graph, together with the SpO_2 targets, while the current measurements are displayed numerically. Generating advice on the adjustment of the FiO_2 seems possible by using a predictor, but due to lack of information about applied ventilation, implementation of this advice is currently not possible.

CONCLUSION: With the aid of the user interface of the ASOR, control of the SpO_2 should improve, because the deviation from the targets and trends (higher order dynamics) can be instantly seen. However, the uncertainty about the adequateness of the ventilation prohibits the development and implementation of an advisory system.

INTRODUCTION

Due to immature lungs, preterm infants often require supplemental oxygen during resuscitation after birth. Resuscitation is a period in which multiple staff members are focused on stabilizing the infant.

During resuscitation, supplemental oxygen therapy is guided by the measured pulse rate and oxygen saturation (SpO_2). At the end of 2010, the European Resuscitation Council (ERC) [1], American Heart Association [2] and Australian Resuscitation Council and New Zealand Resuscitation Council [3] published new guidelines on neonatal resuscitation, in which SpO_2 targets were introduced to guide supplemental oxygen therapy. These targets are based on an observational study by Dawson et al. [4], in which the reference values of both heart rate and SpO_2 were determined, in healthy infants that did not require respiratory support during their resuscitation. The SpO_2 targets from the ERC guidelines [1] are the 25th centile of the observational study conducted by Dawson et al. [4]. The targets form a gradually rising curve, from 60% SpO_2 at 2 minutes after birth, to 90% SpO_2 at 10 minutes after birth (Figure 6 page 26).

Following these saturation targets is challenging, because of the immaturity of the infants [5, 6], the drawbacks of pulse oximetry [6, 7] and the lack of an unambiguous relation between the fraction of inspired oxygen (FiO_2) and SpO_2 [8, 9]. Furthermore, the guidelines give no information on how to adjust the FiO_2 in order to control the SpO_2. Due to earlier mentioned difficulties the deviations from the SpO_2 targets are large during routine resuscitations. An observational study of 78 preterm infants showed an average deviations of 7.8% SpO_2 (IQR 5.8 – 12.5% SpO_2) from the saturation targets during the first 10 minutes after birth (Chapter 2; Observing the resuscitation of very preterm infants; Are we able to follow the oxygen saturation targets?).

Because the devices used are not designed specifically for resuscitations, a number of separate devices are needed to provide the information that is needed to control the SpO_2, and they are often placed at various locations around the resuscitation bed. An additional challenge is that the measurements are displayed numerically, so there is no way to observe trends.

By displaying measured parameters in graphs, it becomes easier to assess the higher order dynamics, which improves the controllability. How large this benefit is depends among others on the frequency of the signal, the scale of the graph, measurement interval and the amount of attention that can be given to the control (Appendix A.3; Human control theory).

Alarms, relevance and noise pollution

The pulse oximeters that are currently available and needed to monitor the SpO_2 during resuscitations are not specially designed for this task. They are primarily meant for an intensive care unit (ICU), where the settings are seldom changed, and the SpO_2 is meant to stay between a fixed upper and lower limit. However during resuscitations the SpO_2 and heart rate are meant to rise [1].

The reference values determined by Dawson et al. [4] (the study on which the ERC SpO_2 targets are based [1]) suggest that many healthy infants have heart rates < 100 bpm at 1 min after birth, and 21% of the infants still had a heart rate lower than 100 bpm after 2 min. For SpO_2, the study reported measured values around 50 – 55% at 3 – 5 minutes, 65 – 75% at 7 – 8 minutes, and > 85% after 10 minutes of life. The mean time to reach SpO_2 values >90% was 7.9 minutes. This means that, on average, there will be 1 low pulse rate alarm and 7 low saturation alarms during the resuscitation of an average infant, which is considered to be healthy and does not need respiratory support. Therefore, the settings of alarms should be dependent on the time of birth instead of the current fixed alarm settings during the entire resuscitation.

A large problem with giving alarms during the first minutes of resuscitation is that when most of these alarms occur, the physician will already be working to correct the problem. This makes the alarm redundant and annoying to the staff. An alarm should attract attention to a potentially dangerous event that would otherwise go unnoticed, be relevant, be unique, have priority, be accompanied with a descriptive text and diagnosis, and advise on how to correct the event [10]. The current alarms of the pulse oximeter fail almost all of these requirements, especially during the first 10 minutes after birth in which the SpO_2 is meant to rise. However, the removal of all alarms from the resuscitation area is not the solution either. For example, in the situation when a patient deteriorates rapidly after an initial stable period, his initial stable period might dull the physician into a falls sense of security, and in these circumstances an alarm is necessary.

To properly deal with the problem described above, it is necessary to know whether a problem is being addressed or not. Currently, there are not enough parameters measured to properly judge this. By adding parameters that judge the ventilation, and combining all measurements in one device, a better assessment can be made about if a problem is being dealt with. As a consequence alarms can be automatically suppressed when this is the case. The inclusion of parameters related to ventilation has the added benefit that it will enable a system to give a better description of the cause of the alarm and advise the physician on how to solve the problem.

By making the intensity of an alarm time dependent, the noise pollution can be reduced further. An alarm can start with just visual cues (blinking), and transfer to an audible alarm after a set period, with increasing volume. The time scale must be appropriate for the cause of the alarm, and should ensure that someone is warned within the appropriate time, to avoid any additional risks [10].

The aim of this study was to develop a device that would aid the clinicians during resuscitations, and help reduce the deviation from the SpO_2 targets. In a cooperation between the Erasmus Medical Centre (Rotterdam, The Netherlands) and the Delft University of Technology (Delft, The Netherlands), the Advisory System for Oxygen during Resuscitation (ASOR) was developed, a system that by a new representation of the data and advice on FiO_2 adjustment, should improve SpO_2 control.

METHODS

The main focus of the ASOR is the new graphical interface that combines all relevant parameters (pulse rate, SpO_2, FiO_2, and time after birth) in relation to the SpO_2 targets. The ASOR was developed in Labview 2011 (National Instruments, Austin, Texas, USA), because of the ability to run a single program multithreaded, and the robustness and ease of its data acquisition.

Design

As part of the design process, interviews were conducted with the clinical staff of the Erasmus Medical Centre (Appendix A.4; Interviews with clinical staff). In these interviews, the clinical staff was asked about their preferences and their association with both location and colour use for the different parameters.

The colours used for the ASOR were chosen in accordance with NPR 7022: Functional use of colour - accommodating colour vision disorders [11], which should ensure that it is clear for all users. The easiest way to ensure that the parameters are distinguishable is to ensure enough difference in contrast, which can be checked by converting an image to grayscale. When the distinction can be made in grayscale, it can be made by everyone, no matter what type of colour vision disorder he or she may have.

Alarms

The SpO_2 alarms were improved by including the SpO_2 targets (ERC 2010 [1]), time after birth, and FiO_2 as variables. The inclusion of the time after birth and SpO_2 targets means that during the first 10 minutes the high and low saturation alarms can be made dependent on the targets. The acceptable variation around the target that is acceptable is yet to be determined, since the current guidelines give no advice. Logical choices would be plus or minus a fixed deviation, or to use percentiles from the study the targets are based upon [4].

Advice

One of the difficulties with the manual adjustment of the FiO_2 in order to control the SpO_2, is the ambiguous relation between FiO_2 and SpO_2. The relation between SpO_2 and FiO_2 is e.g. dependent on the infants' condition, and is nonlinear due to the relation between partial pressure of arterial oxygen (PaO_2) and SpO_2.

A possible way to improve the control is with an advisory system. Such a system would calculate advice on when and how to adjust the FiO_2 in order to control the SpO_2, based on the measured parameters, and provide this advice to the physician. The advice can be improved with the use of averaging and the use of prediction. Averaging would make the system slower but more stable. Prediction on the other hand would speed up the system, by using the rate of change (speed) of the measured SpO_2 to predict the SpO_2 in the future, but would increase the likelihood of errors.
A prediction can be made visible by the use of a predictive display. In a graph this is done by drawing a line from the current value to the predicted value [12]. When a prediction is used as the basis for advice, the benefit of using a predictive display is that the basis of the prediction can be seen. When the calculated prediction can be seen, it is easier to assess the correctness of the advice which will help the users gain faith in the device. The downside is that it would add additional information, the averaged SpO_2 and the prediction, to the graph displayed of the ASOR.

In comparison to an automated closed loop system, an advisory system needs to be more stable, because rapid changes in advice would overwhelm the physician. The interval with which advice can be given is low, otherwise the physician is unable to judge and carry out the given advice. This will inevitably result in a reduced performance when it comes to controlling the SpO_2, compared to an automated closed loop system.

RESULTS

The ASOR was made as a separate program to run under Windows (Microsoft, Redmond, Washington, USA) on a generic computer. A touchscreen was used as the input device, in order to easily control the program. None of the standard equipment needed to be replaced but some minor adjustments were necessary.

Experimental setup

The pulse oximeter used was a Nellcor N-600x, from which the measured SpO_2 and pulse rate were read via serial port. To obtain information on the FiO_2, an oxygen sensor was placed into the oxygen blenders bleed flow port. A detailed list of all equipment used can be found in Table 4.

Table 4: Equipment used as part of the ASOR.

Product	Brand and Version	Manufacturer	Location
Pulse oximeter*	OxiMax N-600x	Covidien - Nellcor	Boulder, Colorado, USA
Pulse oximetry sensor*	OxiMax Max-N	Covidien - Nellcor	Boulder, Colorado, USA
Oxygen blender*	Bird Ultrablender	Cardinal Health	Dublin, OH, USA
Oxygen analyser	MX300 Medical Oxygen Monitor	Teledyne Technologies	City of Industry, California, USA
Oxygen sensor	AdQuipment Oxygencel M-15 STD	IT Dr. Gambert GmbH	Wismar, Germany
Serial to USB converter	UPort 1410	Moxa	Taipei City, Taiwan
Software	Labview 2011 Version 11.0	National Instruments	Austin, Texas, USA
Laptop	Asus UL30AWindows	ASUSTeK computer Inc.	Taipei City, Taiwan
Operating system	Windows 7 Home Premium Service Pack 1	Microsoft Corperation	Redmond, Washington, USA
Touchscreen	Generic 8 inch touchscreen (800x600)	unknown	
Isolating transformer	KLMX/S-320-230/230	Muuntosähkö Oy - Trafox	Helsinki, Finland

Equipment marked with * is part of the standard equipment, the rest is added as part of this study.

Design

Most of the minor design aspects were the result of the use of Labview's "Silver Controls" palette, which placed some small limitations on the visual design, but no significant compromises had to be made. The centre of the visual design of the ASOR is the graph that displays the pulse rate, SpO_2, FiO_2 and target SpO_2, over the last 10 minutes (Figure 4). Because of the expected ranges, the different parameters could be plotted in one graph with a minimal change of interference with each other (Table 5). By plotting them together in a single graph, the screen size can be optimally used, ensuring a clear representation of the data on a relatively small screen. There is, however, a possibility that the pulse rate or SpO_2 and FiO_2 overlap and/or cross. To make it easy to distinguish, the area under the FiO_2 line is filled until the x-axis, setting it apart from the measured patient data [13]. The sequence of plotting ensures that the most important parameter is always plotted on top (Table 5), so it can always be seen clearly. The measured parameters are displayed numerically next to the graph, so that the exact value can easily be read, a feature requested by the majority of the staff.

The interviewed clinical staff had a clear preference for the pulse rate in the top right corner, and a slight preference for the colour red for pulse rate and blue for SpO$_2$. More important for the staff was that the layout and use of colour is the same as used by other monitoring equipment displaying the same parameters, to limit confusion.

Table 5: The variables displayed in the graph on the ASOR.

Variables	Expected Range
Pulse rate	80-200 bpm
SpO$_2$	40-100%
Target SpO$_2$	60-93% (85-93% after 10 minutes)
FiO$_2$	21-100%

Table is in order of plotting (first is plotted on top) and with their expected range.
bpm = beats per minute, FiO$_2$ = fraction of inspired oxygen, SpO$_2$ = oxygen saturation.

The colours used in the ASOR were chosen in accordance with NPR 7022: Functional use of colour - accommodating colour vision disorders [11]. Figure 4 shows the result in both colour and grayscale, the easiest way to ensure that the ASOR is usable for people with colour vision disorders. The limited possibility of the different variables to cross, further limits the changes of misinterpreting variables.
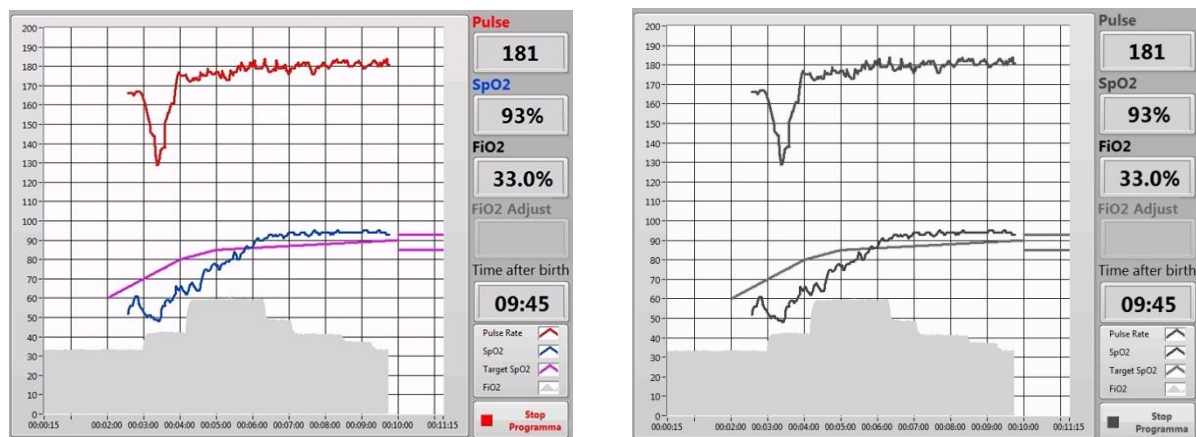
Figure 4: The visual design of the ASOR, suitable for colour blind people.
The visual design is done in accordance to NPR 7022, to ensure it is clear for people with a colour vision disorder. This can be checked by taking the display (left) and changing it to grayscale (right). Pulse rate, oxygen saturation (SpO$_2$), target SpO$_2$, and fraction of inspired oxygen (FiO$_2$) are plotted together in a single graph. The numerical values of all measurements are displayed on the right hand side of the screen.

The ASOR is started at birth (APGAR time), displaying the target SpO$_2$ from the ERC guidelines, and the NICU SpO$_2$ levels, for the next 11 minutes (Figure 5 left). After the first 10 minutes after birth have passed, the time axis starts to scroll, always showing the last 10 minutes, and 1 minute ahead (Figure 5). This was done so that the current data is not plotted on the edge of the graph. An interval of ten minutes was chosen as a good trade-off between observed time, scale, resolution, and available screen size.
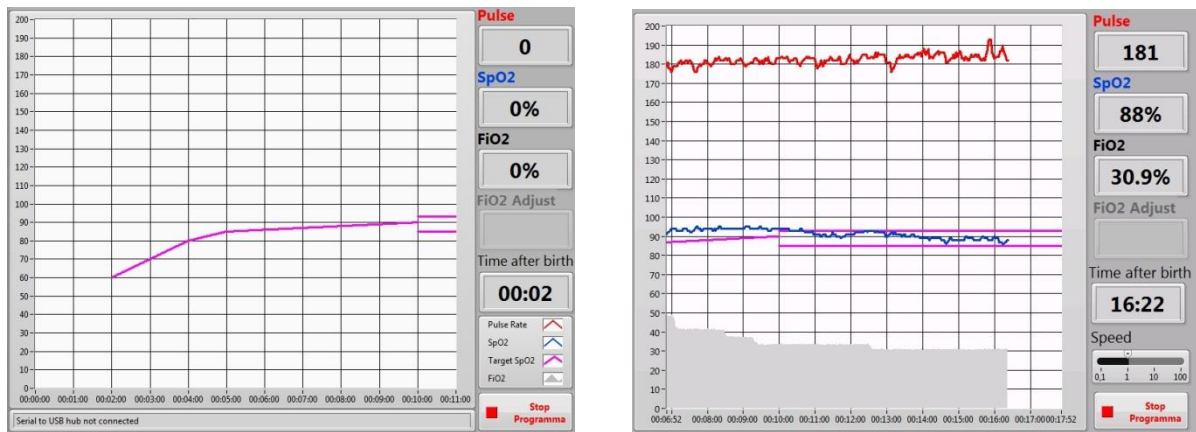
Figure 5: Plotting of the measurements and oxygen saturation targets depending on time after birth. When the resuscitation is started the ASOR plots the target SpO$_2$ for the first 11 minutes after birth (left). After the first 10 minutes the time axis rolls, so that the last 10 minutes are always displayed, and new data is not plotted on the edge of the graph (right).

Alarms

The frequency of false alarms has resulted in a general ignoring of alarms during resuscitations. In an interview conducted amongst the clinical staff of the Erasmus MC, 8/10 indicated that they ignore the alarms during the first 10 minutes of the resuscitation of preterm infants. All alarms are suppressed immediately by someone from the nursing staff. The majority of the interviewees said that they did not need a saturation alarm at all during the first minutes of resuscitation, because they are already focused on the oxygen saturation (Appendix A.4; Interview with the clinical staff).

The ASOR was currently designed to work parallel to the existing equipment. For safety reasons, it was not possible, nor desirable, to replace the current equipment until proper function of the ASOR can be guaranteed. Until it does replace the existing equipment, it is not possible to replace any of the existing alarms and new alarms would only be an additional annoyance. Therefore, the choice was made to only add visual alarms, in the form of blinking indicators on the display. This will attract the physician's attention without adding more noise pollution to the resuscitation room.
When the ASOR does replace the current equipment, the goal is to prevent the large number of false alarms generated during the first 10 minutes, and a clear indication is given on what the cause of the alarm is when one does trigger. This is done by combining the measured SpO$_2$ with the targets, and time after birth.

When the saturation is outside the alarm limits (Figure 6), the saturation field starts to blink between its grey background colour and red, at a rate of 1 Hz. When the pulse rate is below 100 bpm, the low pulse rate alarm triggers, and the background of the pulse rate field blinks. The alarms only initiate after a measurement is obtained. If, after 2 minutes after birth, there is still no measurement at all, the background of both the saturation and pulse rate turn red, to indicate a problem with the pulse oximeter (sensor). A description of the alarm is given in a textbox at the bottom of the screen (Figure 5 page 27).

The alarm limits during the first 10 minutes were set to ±5% from the ERC targets, to provide a similar bandwidth as the NICU targets. The chosen alarm settings are more conservative than the other option, namely the use of the 10th and 50th centile of the study by Dawson et al. [4] on which the guideline is based, as advised by a number of experts [14]. A visual representation of the SpO_2 alarm settings of the ASOR, as used in the Erasmus Medical Centre, is displayed in Figure 6. The high saturation alarm is meant to prevent hyperoxia, and should urge the user to dial back the FiO_2. This alarm is only useful when additional oxygen ($FiO_2 > 21\%$) is administered, and thus is turned off if no additional oxygen is given.
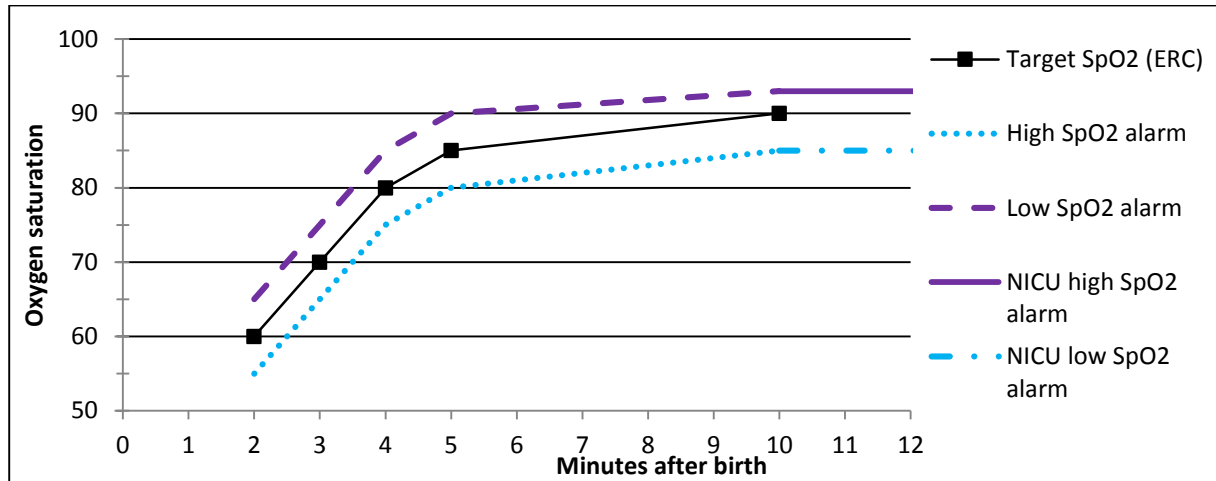
Figure 6: Alarm settings as used in the ASOR for clinical trials preformed at the Erasmus Medical Centre (Rotterdam, the Netherlands).
High and low oxygen saturation (SpO_2) alarms are based on the target SpO_2 levels from the European resuscitation council (ERC) guidelines 2010 [1]. The low pulse rate alarm is set to 100 beats per minute, in accordance with the guidelines used within the Erasmus Medical Centre.

Advice
In order to give stable advice, the measured SpO_2 was averaged using a moving exponential average over the last 20 seconds. The exponential moving average gave better results, with the same averaging time, than a normal moving average, because the weighting for each older data point decreases exponentially (2).

$$Y_i = \frac{N-1}{N} Y_{i-1} + \frac{1}{N} X_i \qquad (2)$$

X_i is the result of the analysis performed on the i-th block, Y_i is the result of the averaging process from X_1 to X_i, N = the number of points over which is averaged [15].

The advice given by the ASOR is improved by the addition of a predictor. Based on the speed difference between the target and the measured SpO_2 and the acceleration of the measured SpO_2, the error between target and measured SpO_2 was predicted 30 seconds into the future. This prediction was incorporated in the advisory system, and used to predict when the SpO_2 will be on target, and if it will overshoot the target. When the measured error is zero but the predictor shows the SpO_2 will deviate from the target, a fixed error of 5% is assigned in order to calculate the FiO_2 adjustment. The complete control scheme can be found in the appendix, page U, Table 12: The structure, rules and corresponding actions of the advice module of the ASOR, based on proportional control.

Averaging and predicting the SpO_2 showed promising results when simulating advice on adjusting the FiO_2. However, a large uncertainty remained: the applied ventilation. If the ventilation is inadequate, it should be adjusted first, before adjustments to the FiO_2 are advised in order to control the SpO_2. Adjustments to the mask placement, positive end expiratory pressure (PEEP) and/or peak inspiratory pressure (PIP) might be needed to better aerate the lungs. Without measurement of the administered pressures and flow, and the resultant inspiratory and expiratory volumes, it is impossible to assess if the ventilation is adequate. Until then it is unethical to give advice on adjusting the FiO_2. More on detecting ventilation, giving FiO_2 adjustment advice and work that is needed to guarantee the correctness of the advice can be found in chapter 5: Improving advice "Detection of proper ventilation" on page 47.

DISCUSSION

By combining the parameters needed to control the SpO_2 and displaying it on a single screen, the administration of oxygen therapy during resuscitation is simplified. The plotting of the measured SpO_2 in combination with the SpO_2 targets should be an incentive to minimize the error. The ability to see trends and the FiO_2 that has been given thus far should help with assessing the FiO_2 adjustments that are needed to keep the SpO_2 on target.

The current ASOR design is one of many possible user interfaces. Although physicians were asked to give their opinion on the design during the development, most of them had trouble imagining the details of such a device, and therefore could not properly comment on their preferences. Even with the current design of the ASOR and its use in the clinic, it is difficult for most to comment on design details. The main difficulty in commenting on the design is the novelty of the ASOR. It is clear that there is a learning curve for the physicians in order to get used to the ASOR and its interface.

The alarm limits during the first 10 minutes were set to ±5% from the ERC targets. In retrospect, it would have been better to use the 10th and 50th centile of the study by Dawson et al. [4]. These percentiles would give a decreasing allowable deviation from the target. Such a narrowing bandwidth of acceptable SpO_2 values would be a better representation of the large variation of initial SpO_2 values that are observed, and would coincide with the increase in ability to control the SpO_2 as time after birth increases. (See chapter 2: Observing the resuscitation of very preterm infants; Are we able to follow the oxygen saturation targets?). Additionally, the larger acceptable deviation would further reduce the number of alarms. It remains to be determined whether a larger spread in acceptable deviation would increase the overall observed variation, or if it will reduce the overall variation because it will be easier to stay within the larger bandwidth.

The lack of information about ventilation prohibits the advice on FiO_2 adjustments. If, and if so, to what extent the ASOR would improve the control over the SpO_2 remains to be tested. Results of a pilot test conducted at the Erasmus Medical Centre (Rotterdam, the Netherlands) are described in Chapter 4. A benefit of a system determining the adjustment of FiO_2, is that, when the advice is followed, the control strategy is standardized. Standardization of the control strategy will make comparison between different targets or approaches more reliable, because it eliminates one of the variables.

Developing the ASOR, with display of all parameters and their trends on a single screen, could be an aid in controlling SpO_2 during resuscitation. The next step is to test the ASOR in its clinical application, by providing the physicians with information during the resuscitation of preterm infants. The results of this study can be read in the next chapter: "The results of using the ASOR during the resuscitation of preterm infants".

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4. The results of using the ASOR during the resuscitation of preterm infants

T.G. Goos[12], D. Rook[2], A.C. van der Eijk[12], A.A. Kroon[2], J. Dankelman[1], I.K.M. Reiss[2]

[1] Department of BioMedical Engineering, Faculty of Mechanical, Maritime and Materials Engineering, Delft University of Technology, Delft, The Netherlands
[2] Department of Paediatrics, Division of Neonatology, Erasmus Medical Centre - Sophia Children's Hospital, Rotterdam, The Netherlands.

ABSTRACT

BACKGROUND: The European Resuscitation Council (ERC) guidelines prescribe oxygen saturation (SpO_2) targets for the first 10 minutes of resuscitation after birth. Unfortunately, the control of SpO_2 in newborn infants is difficult.

OBJECTIVES: To determine whether a new graphical interface (the ASOR), reduced deviation from SpO_2 targets during resuscitation of preterm infants after birth.

METHODS: In a single-centre study, the deviation from the SpO_2 targets during resuscitation of preterm infants (gestational age (GA) ≤30 weeks) with the aid of the ASOR was compared with current clinical practice (control group). The ASOR displays all relevant parameters on a single screen, and their trend lines together with their target. Data presented as median (IQR).

RESULTS: Twenty-five infants (GA $27^3/_7$ (26–$28^4/_7$) weeks, birth weight (BW) 880g (778–1040)) were resuscitated using the ASOR and 78 infants (GA $27^4/_7$ (26–$28^6/_7$) weeks, BW 945g (780–1140)) were included in the control group. Overall infants that were resuscitated with the ASOR spent less time above the SpO_2 targets (19% (11–31) vs. 25% (11–40)), and had a smaller deviation during the time spent above the SpO_2 targets (2.9%SpO_2 (1.2–4.7) vs. 3.6%SpO_2 (2.4–5.4)). Both time spent below the SpO_2 targets (28% (19–38) vs. 26% (14–39)), and deviation below the target (6.9%SpO_2 (5.1–8.5) vs. 7.3%SpO_2 (3.2–13.4)) remained similar. After the first 10 minutes there was a significant reduction in time spent above the high SpO_2 target (3% (0–14) vs. 11% (0–27), p=0.037 Mann Whitney U-test) when the ASOR was used.

CONCLUSION: The use of a new graphical interface significantly decreased high SpO_2 levels during the resuscitation of preterm infants. However, both time spent below and deviation below the SpO_2 targets did not change significantly. The display of trend data together with the targets does increase the awareness of deviations from the target, but does not increase the controllability. It appears that the current ERC targets are interpreted as the maximum acceptable SpO_2, a target range would clarify the acceptable deviation.

INTRODUCTION

SpO_2 control during the resuscitation after birth is a delicate balance between avoiding both hypo and hyperoxia. Hyperoxia can result in the formation of excessive oxygen free radicals, which can potentially harm the organs. It has been shown that even short exposure to high oxygen concentrations in the first minutes after birth may have detrimental effects on newborn infants [1]. However, an increase in oxygen saturation and with that a certain level of oxidative stress, is needed to initiate the cardiopulmonary adaptation during transition to extra uterine life [2, 3].

To prevent negative outcomes due to under or over exposure to oxygen in newborn infants, both the guidelines of the European Resuscitation Council (ERC) [4]and American Heart Association (AHA) [5] prescribe oxygen saturation measured by pulse oximetry (SpO_2) targets for the first 10 minutes after birth.

The SpO_2 targets in the ERC guidelines are based on the 25th percentile of the SpO_2 values obtained in a study by Dawson et al. [6]. In this study normative values of heart rate and SpO_2 were obtained in 468 healthy, mostly term infants who did not require respiratory support during resuscitation. Although the ERC gives target SpO_2 levels at specific times after birth, no advice is provided on how these targets should be achieved. Currently, to reach and maintain the target levels for SpO_2, the fraction of inspired oxygen (FiO_2) is adjusted manually by the physician. This manual control is difficult due to underdevelopment of the organs like the lungs and brain [7, 8]. Furthermore, pulse oximetry is known to be influenced by movement and low blood perfusion [8, 9]. We previously demonstrated in an observational study that deviations from the SpO_2 targets are large and frequent during the resuscitation of preterm infants (Chapter 2: Observing the resuscitation of very preterm infants; Are we able to follow the oxygen saturation targets?).

We hypothesized that by displaying the trend of the parameters involved in oxygen therapy (SpO_2, pulse rate and FiO_2) together with the SpO_2 targets, the physician will be able to better follow the SpO_2 targets, and reduce variation. Therefore, the aim of this study was to compare the newly developed ASOR (Advisory System for Oxygen during Resuscitation) with current clinical practice during the resuscitation of preterm infants.

METHODS

This study was performed in the Erasmus Medical Centre (Rotterdam, the Netherlands), a level-III-c neonatal intensive care unit (NICU) with 33 beds [11]. The study was judged by the medical ethics committee of the Erasmus Medical Centre not to be subjected to the Medical Research Involving Human Subjects Act (WMO) [10]. The medical ethical application can be found in the Appendix page SS; "Research protocol: Advisory System for Supplemental Oxygen Therapy during Resuscitation of preterm infants".

Subjects

Infants born in the study centre with a gestational age (GA) ≤30 weeks were eligible for this study. Infants with any known congenital or chromosomal defects were excluded from this study. Infants were resuscitated with the aid of the ASOR when a researcher was available at the time of birth. Other infants were included in the control group.

Resuscitation

According to the local protocol, preterm infants were transferred to the resuscitation unit immediately after delivery, where at least 2 clinicians start to stabilize the infant. Resuscitations of infants <26 weeks GA are performed by neonatologist or neonatal fellows. Measures were taken to prevent heat loss. Respiratory support was given, primarily with a T-piece resuscitator (Neopuff, Fisher & Paykel Healthcare, Auckland, New Zealand). A flow-inflating bag with pressure monitoring (Jackson Reese modification T-piece breathing system, Intersurgical, Wokingham, UK) was also available and could be used according to the physician's preferences. Local protocol advises to start resuscitation with room air (21% FiO_2)for infants with a GA >28 weeks and with a FiO_2 of 30% for infants with a GA ≤28 weeks (based on publications by Escrig et al., Vento et al. and Saugstad et al.[11-13]). Furthermore, FiO_2 should not be adjusted before an SpO_2 measurement is obtained, unless the pulse rate drops below 100 beats per minute (bpm)[4]. A pulse oximeter sensor (Nellcor OxiMax Max-N, Covidien, Boulder, USA) was placed on the right hand or wrist to measure preductal SpO_2[14].

During the first 10 minutes after birth, the SpO_2 targets from the ERC guidelines were prescribed, i.e. 60%, 70%, 80%, 85%, and 90% at 2, 3, 4, 5, and 10 minutes after birth, respectively. From the 10th minute onwards, the target range of the study centre's NICU were prescribed (85-93% SpO_2)[15]. When respiration was absent or insufficient, ventilation was initiated with sustained inflations, i.e. 5 inflations of 3 seconds, after which respiratory support could be optimised by adjusting the positive end expiratory pressure (PEEP) and/or peak inspiratory pressure (PIP) (initially set to 5 and 20 cmH_2O respectively). When respiration of the infants remained insufficient or if the infants remained hypoxic, endotracheal intubation was performed.

The ERC guidelines were introduced 7 months prior to the start of this study. They were discussed amongst the staff prior to being adapted as the local resuscitation protocol, and are part of the education of residents physicians. The SpO_2 targets were available in all resuscitation areas, together with a Dutch translation of the ERC 'Newborn life support algorithm' [16].

The infants resuscitated with the aid of the ASOR received the same standard care. The only addition was the visualization of their pulse rate, SpO_2 and FiO_2 together with the SpO_2 targets on the ASOR.

ASOR equipment

A detailed list of all equipment used can be found in Table 6, and an overview of the setup in the Appendix page Y: Figure 23: Equipment used for the ASOR version 1, and how it is interconnected. All electronics added as part of this study were connected to an isolating transformer in order to guarantee electronic safety.

Table 6: Equipment used as part of the ASOR.

Product	Brand and Version	Manufacturer	Location
Pulse oximeter*	OxiMax N-600x	Covidien - Nellcor	Boulder, Colorado, USA
Pulse oximetry sensor*	OxiMax Max-N	Covidien - Nellcor	Boulder, Colorado, USA
Oxygen blender*	Bird Ultrablender	Cardinal Health	Dublin, Ohio, USA
Oxygen analyser	MX300 Medical Oxygen Monitor	Teledyne Technologies	City of Industry, California, USA
Oxygen sensor	AdQuipment Oxygencel M-15 STD	IT Dr. Gambert GmbH	Wismar, Germany
Serial to USB converter	UPort 1410	Moxa	Taipei City, Taiwan
Software	Labview 2011 Version 11.0	National Instruments	Austin, Texas, USA
Laptop	Asus UL30AWindows	ASUSTeK computer Inc.	Taipei City, Taiwan
Operating system	Windows 7 Home Premium Service Pack 1	Microsoft Corporation	Redmond, Washington, USA
Touchscreen	Generic 8 inch touchscreen (800x600)	unknown	
Isolating transformer	KLMX/S-320-230/230	Muuntosähkö Oy - Trafox	Helsinki, Finland

Equipment marked with * is part of the standard equipment, the rest is added as part of this study.

The ASOR is designed to work in parallel with the existing equipment. This is primarily done for safety reasons; in case of a failure or malfunction of the ASOR, the regular equipment can be used to continue the resuscitation. The second reason was to change as little as possible to the physicians' work environment. In critical situations it is important to be familiar with the layout of the work environment [17]. Because the ASOR is not used with all resuscitations, changes are kept to a minimum. The screen of the ASOR is attached to the resuscitation bed in a fixed location, so that it is clearly visible for the physician in charge of the oxygen therapy. The ASOR is started at the same time the APGAR timer is started.

Outcome parameters

The primary outcome was deviation of SpO_2 from a line drawn through the ERC targets and, after the 10th minute, the target range for SpO_2 of the study's NICU. Deviation from the target was assessed by time spent above and below the target, and the average absolute deviation.

$$Average\ absolute\ deviation = \left(\frac{\sum_{measurements\ outside\ range} |target\ SpO_2 - measured\ SpO_2|}{number\ of\ measurements\ outside\ range} \right) \quad (3)$$

This was corrected for the moments when SpO_2 was above the target while no additional oxygen was given (FiO_2=21%), and when SpO_2 was below the target while pure oxygen was administered (FiO_2=100%).

Other parameters that were collected were mode of delivery, administration of antenatal steroids, the reason for preterm delivery, the APGAR scores, the umbilical cord pH and base excess (BE), mode(s) of respiratory support, duration of the resuscitation, FiO_2 administration, and the number of adjustments to the FiO_2 that were made during the resuscitation.

After a resuscitation with the aid of the ASOR, the physician(s) in charge of the oxygen therapy was asked to fill out a questionnaire (Appendix page AA; "Questionnaire after resuscitation with the ASOR; User feedback (in Dutch)").

Sample size and statistics

This study is a pilot study with a limited number of participants. The goal is to study to which extent the ASOR is useful during the resuscitation of preterm infants. A routine resuscitation of a preterm infant lasts about 30 minutes. Within this time period, approximately 10 FiO_2 adjustments are performed. Thus, despite the relative small number of patients included in the study, there will be enough recorded FiO_2 adjustments (±200 adjustments) to determine whether the ASOR will be helpful during resuscitation or not.

To compare this deviation for the group resuscitated with the aid of the ASOR and the control group, a Mann–Whitney U-test is performed comparing the SpO_2 of both groups at specific times after birth (IBM SPSS Statistics 19, Armonk, New York, USA). The Mann–Whitney U test is chosen because of the small sample sizes, and the non-normal distribution of the data. Results are presented as the median (IQR) unless stated otherwise.

RESULTS

Of the 142 preterm births in the course of this study, 93 infants were eligible. Thirty-six infants could not be included because they were either included in another study for which the FiO_2 needed to be blinded [18], or there were problems with the data acquisition (Figure 7). In total, 103 patients were analysed in this study, 78 in the control group and 25 in the ASOR group. Patient characteristics were similar for both groups, although there were more infants born by caesarean section (CS) in the ASOR group (Table 7).
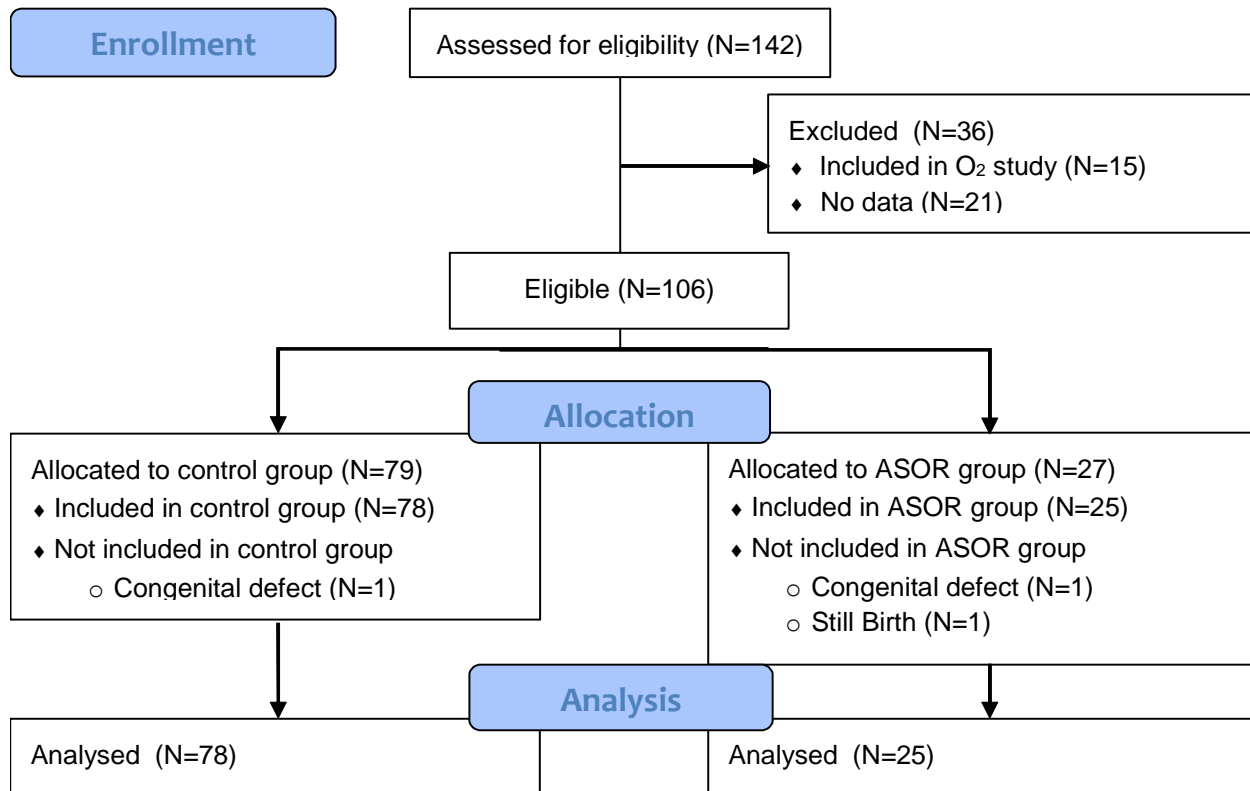
Figure 7: Trial flow.

Table 7: Patients characteristics.

		Control (N=78)	ASOR (N=25)
Patients (N)	male : female	41 : 37	10 : 15
GA (weeks)		$27^4/_7$ ($26–28^6/_7$)	$27^3/_7$ ($26–28^4/_7$)
GA ≤28 weeks (N)		51	15
Birth weight (g)		945 (780–1140)	880 (778–1040)
Reason for preterm delivery	maternal indication	11	5
	fetal indication	31	15
	spontaneous	36	5
Mode of delivery (N)	vaginal : CS	33 : 45	5 : 20
Received full course of corticosteroids (N)		43	18
Cord blood (arterial)	pH	7.31 (7.05–7.48)	7.30 (7.26–7.34)
	BE (mmol/l)	-2.4 (-4.0–-1.45)	-2.0 (-3.0–-1.0)
APGAR score at 5 min after birth		8 (7–9)	8 (6–9)

Data presented as median (IQR). BE = base excess, CS = caesarean section, GA = gestational age.

Control of the oxygen saturation

There was a clear difference in the distribution of the measured SpO_2 between the ASOR group and the control group. The distribution shifted to mostly below the target SpO_2 when the ASOR was used, where in the control group the deviation was distributed around the SpO_2 targets (Figure 8 and Figure 9). With the use of the ASOR the time spent above the target decreased from 25% (11-40) to 19% (11–31) (Table 8). The overall deviation decreased slightly from 6.6% SpO_2 (4.5–9.6) in the control group, to a deviation of 6.2% SpO_2 (5.0–8.1) with the ASOR, while the time spent below the target increased slightly from 26% (14–39), to 28% (19–38) in the ASOR group.

During the first 10 minutes the group resuscitated with the use of the ASOR spent slightly more time above the ERC targets (48% vs. 44%, and during that time had less deviation from them (3.4 vs. 4.4). During the first few minutes almost all of the infants resuscitated with the ASOR had SpO_2 measurements underneath the ERC targets. (Figure 10).

After the first 10 minutes of resuscitation, when the NICU targets were used, there was a significant reduction in time spent above the target with the ASOR (11% to 3%, p=0.037 Mann Whitney U-test), and a decrease of the deviation (1.7%SpO_2 to 1.1%SpO_2). But it was accompanied with a rise in time spent below the target (8% to 11%), with a larger deviation (2.0%SpO_2 to 3.7%SpO_2). The overall time outside the target was smaller for the group that was resuscitated with the use of the ASOR (32% to 27%) (Table 8). After the first 10 minutes, 32% (31–47) of the infants in the control group were outside the NICU targets, with 18% (13–29) above and 17% (12–24) below the target. With the ASOR this changed to 33% (22–67) outside the targets, with 22% (11–33) above and 6% (0–17) below. The usage of FiO_2, and number of FiO_2 adjustments were similar for resuscitations with and without the ASOR.

User feedback

Except for the first, the questionnaire was filled in after each resuscitation with the ASOR. In total, 40 questionnaires were filled in by 21 different users. The most experienced user resuscitated 4 infants with the aid of the ASOR. The questionnaire showed that in 36 occasions (90%) the physician made use of the ASOR during the resuscitation. In 10 of these occasions (25%), the physician looked at the normal saturation monitor before looking at the ASOR, or only looked at the ASOR after the patient had stabilized. On 25 occasions (63%) physicians judged the ASOR to be of assistance in better controlling the SpO_2 during the first 10 minutes, 9 (23%) were unsure. After the first 10 minutes after birth, 20 (50%) (13 (33%) were unsure) thought the ASOR aided them in staying between the alarm limits. On 30 occasions (75%) they found that the use of the ASOR enabled them to better estimate the oxygen requirements of the infant, and in 24 cases (60%) found they had used less oxygen during the resuscitation because of the ASOR.

During the resuscitation of one infant, the FiO_2 was left at 21% during the entire resuscitation; the 2 staff members that did this resuscitation did not adjust the FiO_2, so they found the ASOR did not aid them.

The working was unclear to 4 users (10%) when they first used the ASOR, and 3 (8%) were uncertain. The users thought the ASOR could be improved by using a bigger screen (N=16), better positioning of the screen (N=8) and the use of a larger font (N=2). Gaining more experience (N=16) was the other major comment on how to improve the uses of the ASOR.
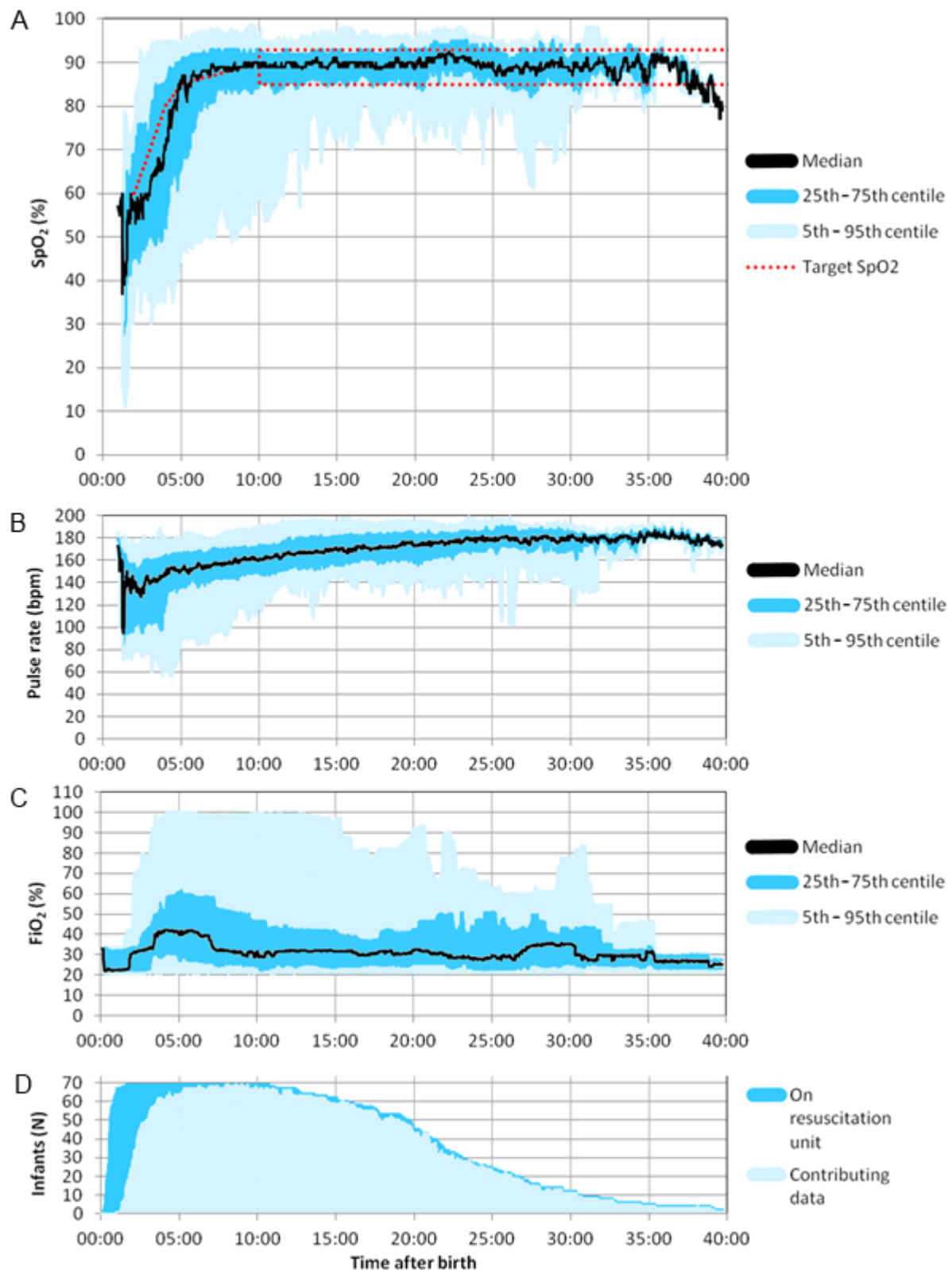
Figure 8: Variation in SpO₂, pulse rate and FiO₂ during resuscitations in the control group.
(A) Median, 5th, 25th, 75th and 95th percentile of the SpO₂ measured during resuscitation, plotted together with the European Resuscitation Council (ERC), and high and low SpO₂ targets, as used at the Erasmus Medical Centre (Rotterdam, the Netherlands). (B) Median, 5th, 25th, 75th and 95th percentile of the measured pulse rate. (C) Median, 5th, 25th, 75th and 95th percentile of the FiO₂ administered during the resuscitation. (D) Number of infants that were on the resuscitation unit at specific times after birth, and number of infants that were contributing to the data set.

Figure 9: Variation in SpO₂, pulse rate and FiO₂ during resuscitations in the ASOR group.
(A) Median, 5th, 25th, 75th and 95th percentile of the SpO₂ measured during resuscitation, plotted together with the European Resuscitation Council (ERC), and high and low SpO₂ targets, as used at the Erasmus Medical Centre (Rotterdam, the Netherlands). (B) Median, 5th, 25th, 75th and 95th percentile of the measured pulse rate. (C) Median, 5th, 25th, 75th and 95th percentile of the FiO₂ administered during the resuscitation. (D) Number of infants that were on the resuscitation unit at specific times after birth, and number of infants that were contributing to the data set.

Figure 10: Variation in SpO₂ during the first 11 minutes of resuscitation, measured in the control group (A), and with the use of the ASOR (B).
Median, 5th, 25th, 75th and 95th percentile of the SpO₂ measured during resuscitation, plotted together with the European Resuscitation Council (ERC), and high and low SpO₂ targets, as used at the Erasmus Medical Centre (Rotterdam, the Netherlands).

Table 8: Comparison of normal practice and resuscitation with the ASOR.

	Control (N=78)	ASOR (N=25)
Total resuscitation time (min)	22:24 (19:08–28:01)	24:18 (19:29–32:10)
SpO$_2$ deviation during the first 10 minutes after birth		
Time above ERC target (%)	44 (12–66)	48 (8–66)
Time below ERC target (%)	51 (27–82)	52 (23–72)
Average deviation above ECR target (%SpO$_2$)	4.4 (1.4–6.5)	3.4 (1.2–5.2)
Average deviation below ECR target (%SpO$_2$)	8.2 (2.8–16.0)	8.3 (4.4–12.1)
Average deviation (%SpO$_2$)	8.2 (5.8–12.5)	7.5 (5.3–11.3)
SpO$_2$ deviation after the first 10 minutes after birth		
Time above NICU limit (%)	11 (0–27)	3 (0–14)
Time below NICU limit (%)	8 (0–23)	11 (2–26)
Time outside of NICU limits (%)	32 (14–46)	27 (9–46)
Average deviation above NICU limit (%SpO$_2$)	1.7 (0.3–2.5)	1.1 (0.0–2.6)
Average deviation below NICU limit (%SpO$_2$)	2.0 (0.0–5.1)	3.7 (1.6–6.2)
Average deviation (%SpO$_2$)	2.6 (1.3–4.5)	3.4 (1.8–5.5)
SpO$_2$ deviation during the entire resuscitation		
Total time above target (%)	25 (11–40)	19 (11–31)*
Total time below target (%)	26 (14–39)	28 (19–38)
Average deviation above target (%SpO$_2$)	3.6 (2.4–5.4)	2.9 (1.2–4.7)
Average deviation below target (%SpO$_2$)	7.3 (3.2–13.4)	6.9 (5.1–8.5)
Average deviation (%SpO$_2$)	6.6 (4.6–9.6)	6.2 (5.0–8.1)
FiO$_2$ adjustments		
Adjustments (N)	7 (3–10)	8 (5–9)
Average FiO$_2$ (%)	33.5 (26.8–44.9)	31.5 (27.1–40.2)
Min FiO$_2$ (%)	21.0 (20.5–22.4)	20.7 (20.3–22.0)
Max FiO$_2$ (%)	59.0 (36.9–99.3)	60.0 (43.0–88.5)
FiO$_2$ at the start of resuscitation (%)	22.5 (21.2–31.8)	22.2 (21.2–31.0)
FiO$_2$ at the end of resuscitation (%)	26.2 (22.2–33.0)	27.5 (21.5–33.2)

Data represented as median (IQR), * = significant at $p < 0.05$.
ECR = European resuscitation council, FiO$_2$ = fraction of inspired oxygen, NICU = neonatal intensive care unit, SpO$_2$ = oxygen saturation.

DISCUSSION

The aim of this study was to assess whether the newly developed ASOR would improve the control of the SpO_2. We hypothesized that the ability to see the trend and higher order terms in the measured data and the target SpO_2 would improve the control of the SpO_2. From this study we cannot simply conclude that the use of the ASOR improved the control over the SpO_2. The reductions in deviation from, and time spend above, the SpO_2 targets highlight the benefit of the ASOR. But, although there was a small reduction in variation of the SpO_2, there was an increase in both deviation and time spend below the SpO_2 targets. Apparently, the physicians interpret the SpO_2 targets, stated in the ERC guidelines as acceptable SpO_2 values, as a maximum, and stay underneath it.

After the first 10 minutes after birth the use of the ASOR resulted in a reduction in time spent above the NICU target, and a reduction in average deviation above the NICU target. This suggests that the ASOR is an aid in reminding the physician to turn down the FiO_2 faster and/or more aggressively.

Since the current ASOR is still in development and does not replace the current equipment, it does not replace any of the alarms. Observations made during this study showed that the physicians did not respond to the visual alarms of the ASOR. Still, the adaption of the SpO_2 alarm limits according to the time after birth, and SpO_2 targets, would greatly reduce the number of false alarms, but they should be audible. Also because the ASOR was only used as part of this study, the layout of the resuscitation bed was not altered. This resulted in physicians looking at the pulse oximeter as a first response, before looking at the ASOR. Furthermore, the small number of patients resuscitated with the ASOR and the high number of staff members at Erasmus Medical Centre, means practice and experience with the ASOR was low.

Because of the nature of this pilot study, i.e. the small study group, users with limited experience with the ASOR, and being conducted at a single centre, it is difficult to draw definite conclusions. The large variation that is normally observed in the control of the SpO_2 during the resuscitation of preterm infants further complicates the interpretation. A larger, and preferably multi centre, study would aid in drawing better conclusions. But in order to test it in multiple centres, the ASOR needs to be approved as a medical device. One large benefit of getting it approved would be that the ASOR could replace the existing equipment, be better positioned, and take over the alarm function.

A drawback of the current setup is the uncertainty of proper ventilation. Currently, the ASOR is unable to measure if an infant is ventilated properly, thus the reason for the deviation from the target cannot be assessed further. By including pressure and flow measurement the ventilation can be assessed. Prior research by Schmölzer et al [19] has shown that by monitoring the pressure and flow, the administration of respiratory support can be improved. The addition of ventilation monitoring would also extend the possibility to improve the alarms and incorporate better advice on how to adjust parameters such as pressure, mask placement and FiO_2 in order to control the SpO_2.

In conclusion the ASOR does have an impact on the control of the SpO_2 during the resuscitation of preterm infants. The significant reduction in time spent above the SpO_2 target, and average deviation above the SpO_2 target are clear improvements. The shift to below the ERC target during the initial 10 minutes is on one hand a good thing indicating that the ASOR does influence the physician and reminds him of the targets, but on the other hand highlights the uncertainty about the targets. A target range instead of single values would take away this uncertainty.

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5. Improving advice

More research on the resuscitation of infants, and particularly preterm infants, is needed. The fact that the current ERC SpO_2 targets are based on a study of only 468 infants with a gestational age (GA) of 38 ± 4 weeks(SD), of which just 160 had a GA < 37 weeks, and none required respiratory support, makes that abundantly clear [1, 2].

Continuation of this study with permanent data collection on the resuscitation of all infants that require respiratory support would greatly enhance the available data, and thereby the accuracy and validity of both the SpO_2 targets and the advice that is given by the ASOR.

Detection of proper ventilation
When advice on the adjustment of the FiO_2 is given, it is important to be certain that the infant is properly ventilated, with a large enough functional residual capacity (FRC) to achieve an adequate gas exchange [3]. Without a proper FRC, increasing the FiO_2 will unnecessarily expose the infant to additional oxygen, with all the associated risks, and only a limited effect on the SpO_2.

Currently, the ASOR has no ability to monitor the ventilation parameters. Therefore it is not possible to assess the ventilation, nor to suspend advice when ventilation is temporarily halted (e.g. during intubation).

Pressure
By adding pressure monitoring to the ASOR, it can detect when ventilation is halted, and halt advice on FiO_2 adjustments until ventilation is resumed. Furthermore, it should be possible to detect leaks between the mask and the infant, a commonly occurring problem [4-6]. The detection of mask leaks will only be possible in combination with the Neopuff (Fisher & Paykel Healthcare, East Tamaki, New Zealand), or similar devices, that have pre-set pressure limits for PEEP and PIP. By comparison of the set and achieved pressures, large leaks can be detected, when there is a failure to reach the pre-set pressure.

Flow and volumes
To assess if an infant is properly ventilated, pressure alone is not enough. Also the flow rate, and thus inspiratory and expiratory tidal volumes, should to be measured. Schmolzer et al. [7, 8] published results of the use of a novel respiratory function monitor. The device continuously displays the pressure, flow, and volume, administered to the infant during resuscitation. They observed a significant reduction in mask leaks, and a lower rate of excessive tidal volume. However, the interpretation of the measurements is left to the physician, which is challenging and time consuming during resuscitation. As stated by Schmolzer et al.: "Doing all of this may have been difficult for some operators. Having another team member observe and interpret the waves and advise the resuscitator might have been more effective" [8].

Pattern recognition could provide a solution here; by only displaying the current pressure and achieved tidal volume, and monitoring the flow and volume patterns in the background, the amount of information that is presented to the physician is limited. This will ensure that it can be interpreted quickly, but because the measurements are monitored by the device, the physician can be warned when certain thresholds are breached or trends are observed. By providing an option to display all relevant parameters, additional information will still be available, and fine tuning of the ventilation can be done when desired.

Near-infrared spectroscopy and Electroencephalography

At least two other measurements might aid the decision making process during resuscitation, and the control of SpO_2 in particular.

Near-infrared spectroscopy (NIRS) is similar to pulse oximetry in the way that is uses the absorption of different wavelengths of infrared light to measure the percentage of haemoglobin that is bonded with oxygen. But contrary to pulse oximetry, it is not dependent on the blood to pulsate in order to measure it. Besides a percentage of oxygen saturation NIRS can be used to quantify blood flow, volume and fractional tissue oxygen extraction (FTOE), by employing several wavelengths and time resolved and/or spatially resolved methods [9]. NIRS can be used to directly measure the oxygenation of the brain, and it has been shown to be useable during resuscitation [10-12]. Kratky et al. [11] concluded that "Our results show that oxygen supply of the brain is provided very quickly although the increase of SpO_2 takes much longer. This might indicate some sort of preference of oxygen supply to the brain compared to other organ systems". Such a preference would make the oxygenation of the brain a much more logical choice to measure compared to SpO_2. Even without such a preference, the use of NIRS would be beneficial, because it would provide an additional parameter to use for determining advice on FiO_2 adjustments and noise cancelation. However, a large problem of NIRS is that the measurement lacks the precision to be used as a quantitative variable and that is dependent on the device. Therefore, only the trend and changes in the measurement can be used [13, 14].

Electroencephalography (EEG) is a measurement of the brain's spontaneous electrical activity. There are no EEG data available of the resuscitation of infants, because it is not possible to measure practically. In order to measure EEG, a large number of leads need to be placed on the infants head. So the usefulness of EEG measurement during resuscitation needs to be explored. New development of a cap incorporating the sensors could make quick application an option, and thus a possibility for measurement during resuscitation.

System identification

System identification was used to model the response of the SpO_2 to a change in FiO_2. With system identification, input and output data are used together with assumptions about the model to fit the parameters of the model in such a way that the model output closely mimics the measured output. When the identified model is a close enough fit, it can be used to predict the response of an infant's SpO_2 to a change in FiO_2. These models were determined with the use of system identification toolbox, from Matlab (R2010a, MathWorks, Natick, Massachusetts, USA.)

Validation

In order to validate the model that is obtained with the use of system identification, data is used that is not part of the dataset that was used to obtain the model [15]. The model is used to both simulate and predict the outcome. (*The difference between prediction and simulation is that in prediction, the past values of outputs used for calculation are measured values while in simulation the outputs are themselves a result of calculation using inputs and initial conditions* [16]) The fit (equation 4) between the simulated or predicted and the measured SpO_2 is used to assess the model.

$$Fit = \left(1 - \frac{|y - \hat{y}|}{|y - \bar{y}|}\right) \times 100 \qquad (4)$$

In this equation, y is the measured output, $\hat{y}$ is the simulated or predicted model output, and $\bar{y}$ is the mean of y. 100% corresponds to a perfect fit, and 0% indicates that the fit is no better than guessing the output to be a constant ($\hat{y} = \bar{y}$) [16].

The confidence interval can be used to assess the stability of the prediction. Where the estimated uncertainty in the model parameters is used to calculate the confidence intervals, and assumes the estimates have a Gaussian distribution [16].

Patient data

In order to simulate the advice on adjusting the FiO_2 and to identify the system, recorded data from the resuscitation of preterm infants was used. To limit the variation, we included infants who were born before 30 weeks of gestation, received additional FiO_2 during their resuscitation, had multiple changes to the FiO_2 and had all changes in the FiO_2 occur while a SpO_2 signal was recorded. For the patients used for the system identification, a response in the SpO_2 needed to be observable whenever the FiO_2 was changed (indicating that there was adequate pressure and no blocked airway), and no intubation attempts were made during the first 15 minutes.

(During intubation a tube is inserted into the trachea, while the ventilation is temporarily halted, resulting in a drop of the SpO_2. In order to obtain a correct model for the SpO_2 - FiO_2 relation during resuscitation, intubation attempts were excluded from the data set used for system identification)

Identification

For the system identification, the error between the target and the measured SpO_2, averaged with the same moving exponential weighted average, was used as the output, the FiO_2 as the input. The use of the error instead of the actual value removes a large portion of the non-linearity from the system, and meant a linear estimation could be made. This does however assume that the SpO_2 targets from the ERC guidelines [2] are correct. If the SpO_2 targets are not correct (in general or for an infant specifically), the system will retain most of its non-linearity. Another effect of which the results are not fully understood is the limits of the SpO_2; It can only rise a few percentage points from the upper limit (40% after two minutes after birth, 7% after the first 10 minutes), while it can fall a lot more (60% at two minutes after birth, 85% after the first 10 minutes). These limitations will influence the system identification process because these limits are not known to the identifier. The patients data used for system identification was selected from the larger set of patient data used to simulate the advice on FiO_2 adjustment (Table 9).

The model is validated by using an additional data recording, of the resuscitation of a preterm infant, which was not used to identify the model.
The resulting optimal model was an ODE 4th order model, with 20 seconds time delay, and 4th order noise;

$$y(t) = [B(q)/F(q)]u(t) + e(t)$$
$$B(q) = -0.03322 \ q^{\wedge}-20 + 0.09555 \ q^{\wedge}-21 - 0.09134 \ q^{\wedge}-22 + 0.02901 \ q^{\wedge}-23$$
$$F(q) = 1 - 2.588 \ q^{\wedge}-1 + 1.821 \ q^{\wedge}-2 + 0.1231 \ q^{\wedge}-3 - 0.3561 \ q^{\wedge}-4 \tag{5}$$

The 20 second time delay is based on observations made of the response time in the collected datasets and the response time of pulse oximeters studied by Baquero et al. [17].

The resulting simulation looks accurate at first glance, with an 85% fit to the recorded data (Figure 11, right). The 99% confidence interval has a ±5% spread in the output (Figure 11, right), which is expectable and even the predicted output behaves stable when it predicts 60 steps in advance (Figure 12, left).
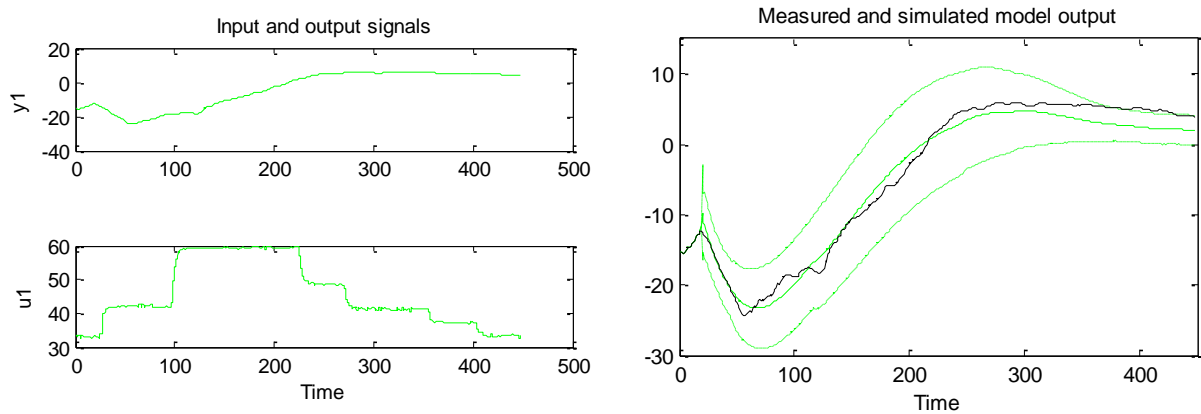
Figure 11: Measured SpO₂ error (left top) and FiO₂ (left bottom) data during the resuscitation of one of the patients, and measured and simulated response on the right.
The response was estimated using an ODE 4th order model, the dotted line indicates the 99% confidence interval.
FiO₂ = fraction of inspired oxygen, SpO₂ = oxygen saturation.

The step response (0 to 1 step) shows an initial negative component, and is very slow to rise to its stable level (Figure 12, right). The rise is so slow that it takes about 400 seconds to stabilize, which means that the effect of most steps performed during the first 10 minutes after birth are not stabilized by the end of the simulation.

Another problem with a model obtained by system identification is that there is no physiological representation, making it impossible to interpret the model, in order to assess if it is correct.
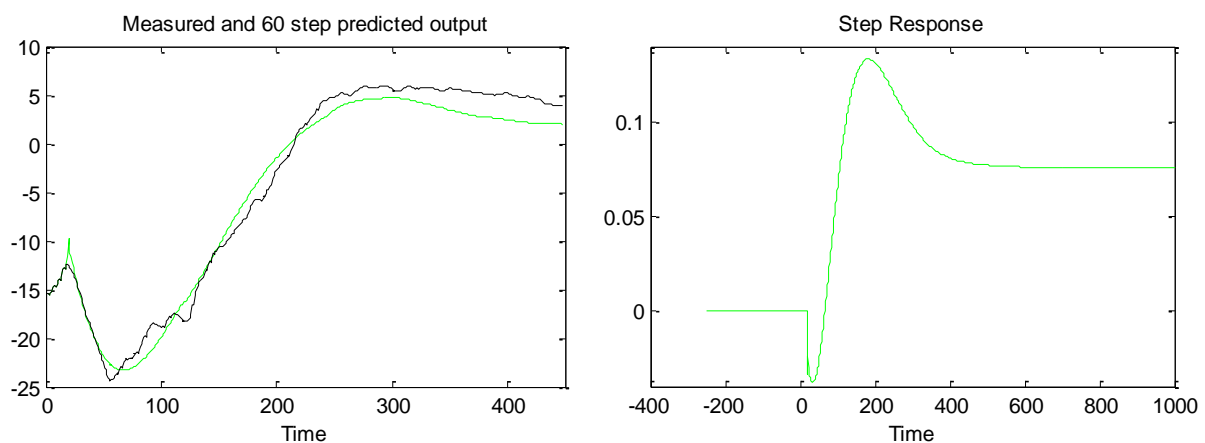
Figure 12: Step response of the obtained ODE 4th order model by system identification.

Attempts at identifying a system as a nonlinear system with just the measured SpO₂ or as a multi input system, by including the pulse rate, did not result in any useful models, which is a further indication that the signal identification is failing, because a clear connection between pulse rate and SpO₂ is known to exist from both a physiological perspective, and from obtained measurements.
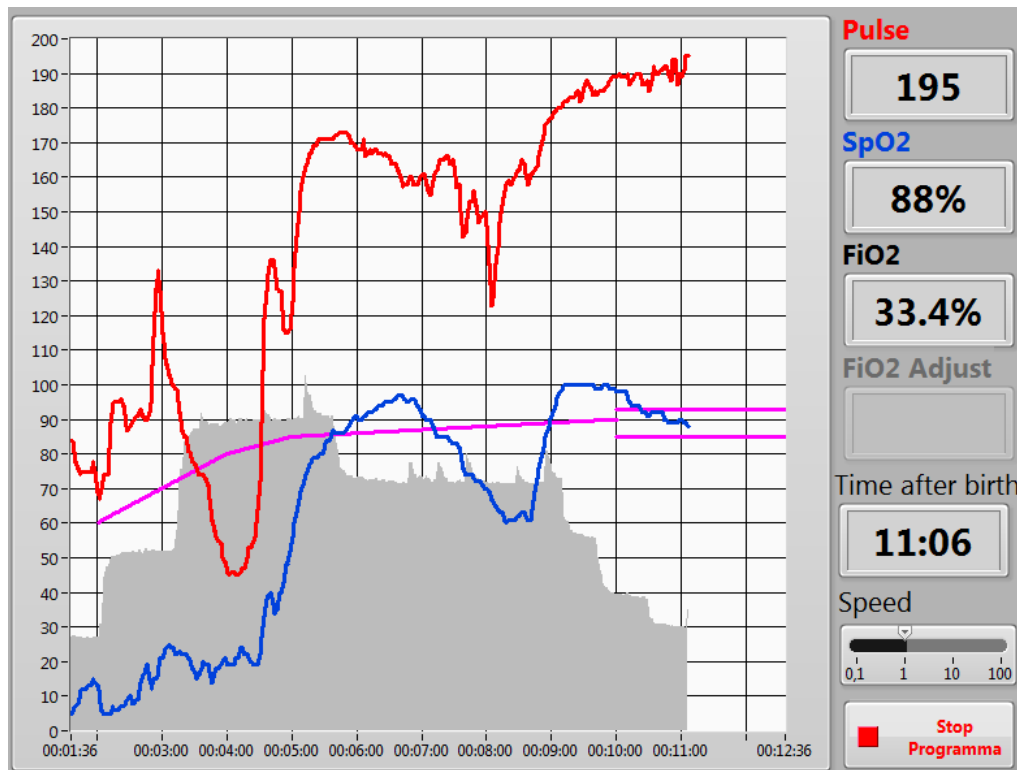
Figure 13: Measured patient data displayed on the ASOR, showing the relation between Pulse rate and oxygen saturation.

From this it can only be concluded that the model identified based on the data that was available thus far is not useful to control the SpO$_2$. More data, and especially longer uninterrupted datasets could make the difference in obtaining a valid model. And a way must be found to include the upper limit of 100% in the system identification process.

Simulating advice on fraction of inspired oxygen adjustment

With the aid of the collected patient data (Table 9), the second version of the ASOR was developed which uses the error between the target and the current SpO$_2$ to advise when and how to adjust the FiO$_2$.

Table 9: Patient characteristics used for simulation and system identification.

	Simulation (N=17)	System identification (N=8)
Gestational Age (weeks)	26.3 (24.4–30.0)	27,29 (24.9–30.9)
Birth weight (g)	920 (450–1600)	900 (450–1675)

Data given as mean (SD).

In order not to overload the physician with data, the averaged SpO$_2$ and predicted SpO$_2$ would not be displayed when the ASOR is in use. The averaging and predictions were displayed during the development and validation of the advice module in order to visualize the process (Figure 14).

Figure 14: Simulation of FiO₂ adjustment advice.
The advice on FiO2 adjustments is based on the proportional error between the target and the measured SpO₂. A form of predictive display is used to visualize how the SpO₂ is changing.
FiO₂ = fraction of inspired oxygen, SpO₂ = oxygen saturation.

Table 10: Parameters in the ASOR that were used to fine tune the advice on when and how the FiO2 should be adjusted.

Parameter	Effect
Averaging time	More stable but slower advice, less fluctuation in FiO₂
Prediction time	A longer time will mean a larger response to the same fluctuation, quicker response to variations, but also more prone to errors and more fluctuations in FiO₂
Target SpO₂ around the ERC guidelines	The amount of deviation from the target that is allowed. A wider band will result in less exposure to FiO₂ and fewer adjustments.
Difference in speed between measured and target SpO₂	The larger the difference needs to be, the quicker the measured SpO₂ will catch up to the target, but a larger difference will increase the chance of overshooting the target
Proportional control	The step size of the FiO₂ adjustment depending on the error between target and measured SpO₂. Dependent on the response of the infant to FiO₂ changes.
Amplification of small steps	Possibility to fine tune the step size. By adjusting the amplification and threshold, the smaller step sizes can be increased.
Correction factor based on current FiO₂	Factor to correct the step size, proportional to the current FiO₂

FiO₂ = fraction of inspired oxygen, SpO₂ = oxygen saturation.

The FiO$_2$ adjustment is calculated based on the error between the target and averaged measured or predicted SpO$_2$, and is scaled depending on the current FiO$_2$. The parameters that were used to fine tune the advice given by the ASOR on when and how to adjust the FiO$_2$ and their effect, are listed in Table 10. The exact scheme of how the advice is determined can be found in the Appendix A.1; The working of the ASOR, Table 13.

Correct advice

In order to assess the advice that is given by the ASOR, simulated advice could be presented to neonatologists and resident physicians. When the advice on the FiO$_2$ changes the physician would be asked if he or she would follow the advice, and if not, what the reason for not following the advice would be. They could also indicate when they would change the FiO$_2$ without the ASOR advising to do so. By doing so, an assessment can be made to what extent the physicians agree with the advice given by the ASOR. This has not yet been done because of the uncertainty of the respiratory support, and thus the advice that is given. Testing now would cost a lot of time and effort from the physicians and researchers, time which could be better used when the uncertainties are dealt with.

INSURING PATIENT SAFETY

A major challenge when developing an automated controller is to ensure patient safety. The only commercially available automated controller, the Avea with $CliO_2$ (by CareFusion, San Diego, USA, CE approved but has yet to obtain FDA approval), limits the changes that can be made to the FiO_2. By limiting the adjustments that can be made to the FiO_2, the damage that can be done is limited. During the resuscitation period these types of safeguards would severely limit the performance, because large variations in FiO_2 are frequently necessary.

The plan is to develop the ASOR as an advisory system, leaving it to the physician to decide whether or not to follow the advice. But even then, the advice given must be correct and the decision model validated in order to ensure patient safety. One of the main concerns with implementing the advice module of the ASOR, is whether the FiO2 needs to be adjusted at all, or if the ventilation is insufficient. When the obtained functional residual capacity (FRC) is inadequate, the FiO_2 should not be increased, but the ventilation should be adjusted.

In order to include the ventilation in the advice module, the pressure and flow should be measured. Research by Schmölzer et al. [7, 8] has shown promising results in monitoring the respiratory function. By including similar measurements in the ASOR, it would be possible to (automatically) assess the ventilation. Such an assessment would improve the accuracy of the advice on adjusting the FiO_2, and would make it possible to include advice on the ventilation parameters, and mask leaks.

The more control a system has, the higher the demands to ensure its safe working, not only from legislation (Appendix A.7; Risk Analysis) but also from the clinical staff that has to work with such a device. Interviews conducted with the clinical staff of the Erasmus Medical Centre (Rotterdam, the Netherlands) have shown that they would be reluctant to follow the advice of a machine (Appendix A4; Interview with the clinical staff). One way to improve both trust in a system as well as safe functioning is to display the values (measured and/or calculated) on which the advice or control is based. This provides the option to check the functioning of the device, by interpreting the values oneself, and deducing a strategy. By comparing that strategy to the strategy of the device, its function can be checked.

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6. Summary and Conclusion

PROBLEM

Preterm infants often need respiratory support during resuscitation directly after birth. This respiratory support consists among others of additional pressure to keep the lungs open and reduce the effort needed to breath, and additional oxygen to ensure an adequate rise of the oxygen saturation (SpO_2) [1]. The SpO_2 is controlled by manually adjusting the fraction of inspired oxygen (FiO_2), in order to follow the SpO_2 targets [2]. The manual control of the SpO_2 has proven to be challenging. Results from the neonatal intensive care unit indicate that only 50% of the time is spent within the SpO_2 range [3-6]. There were no data available on SpO_2 control during resuscitations, but it could be assumed that the control would be a challenge there as well.

The aim of this thesis was to improve the control of the oxygen saturation during the resuscitation of preterm infants immediately after birth. The hypothesis was that by displaying the trends in the measured oxygen saturation, and the target and measured oxygen saturation, control of oxygen saturation would improve. The collected data was to be used to develop and advisory system that advises the physician on when and how to adjust the FiO_2.

In order to map the severity of the deviation from the SpO_2 targets, data were collected during resuscitation of preterm infants. These data (discussed in chapter 2) on the resuscitation of 74 infants, showed the deviation during current clinical practice to be 7.8% SpO_2 (IQR 5.6 - 12.5% SpO_2). Besides the large deviation, it became apparent that there was a lot of overexposure to oxygen, resulting in hyperoxia. Where hypoxia is a condition that needs to be prevented, hyperoxia is a condition purely caused by the administration of too high FiO_2 [7]. The results were published in the journal "Resuscitation".

SOLUTION

To improve the control of the SpO_2 two strategies were chosen. The initial ambitious idea was to develop an automated controller that would control the FiO_2 automatically. To work towards this goal, an advisory system, advising on when and how to adjust the FiO_2 would be developed. However, observations during routine resuscitations made it apparent that a change to the work environment could also be beneficial.

The information needed to control the SpO_2 (pulse rate, SpO_2, FiO_2, SpO_2 targets, time after birth), were displayed on separate devices in different locations. The fragmented information combined with the need to interpolate, in order to follow the SpO_2 targets, and remember how measurements are developing, during the emergency care nature of a resuscitation, makes that simplification welcome, and could result in improved control. The hypothesis was that by combining all the needed information on one single screen and displaying it in such a way that deviations from the target and changes over time would be immediately apparent, would result in a better control over the SpO_2.

DEVELOPMENT

The advisory system and new user interface were combined in the ASOR (**A**dvisory **S**ystem for **O**xygen administration during the **R**esuscitation of preterm infants). (Chapter 3) The initial focus was on the graphical interface, displaying trends and the SpO_2 guidelines that should be followed in one graph. The combined measurements were also used to improve alarms, making it possible to adjust the high and low SpO_2 alarm levels to the SpO_2 targets. Additionally, alarms could be muted when they were incorrect (too high SpO_2 when no additional oxygen is given), and a description of the cause of the alarm was given when an alarm was triggered. Data collected during routine resuscitations were used to develop an advisory system that advises the physician on when and how to adjust the FiO_2.

However, ventilation parameters are not measured during current practice. Because the inspiratory flow and pressure are not measured, there is no guarantee that the infant is ventilated properly. Before the FiO_2 is adjusted the infant should be ventilated properly, and if not, the ventilation should be adjusted (pressure, mask size, mask position, etc.) before the FiO_2 is adjusted. Because of the uncertainty about the ventilation, the choice was made to focus on the graphical interface during the clinical testing, and leave the testing of the advisory system until the measurements of flow and pressure are available.

RESULTS

The ASOR was tested in a pilot study at the Erasmus Medical Centre (Rotterdam, the Netherlands) (Chapter 4). The resuscitation of 25 infants born at a gestational age of 30 weeks or less with the aid of the ASOR was compared to infants resuscitated without the ASOR (control group N=78).
With the usage of the ASOR the overexposure to oxygen was reduced. Both the time spent above the target SpO_2 level and the deviation above the target were significantly less (r=0.008 and r=0.03 respectively). However there was an increase in time spent and deviation below the target (not statistically significant). These results demonstrate that the ASOR does make the clinicians more aware of the SpO_2 targets, but does not significantly reduce the variance around the target. Furthermore, it can be speculated that clinicians are more worried about hyperoxia than they are about hypoxia.

FUTURE

The development of the ASOR and the testing of its functionality will be continued as part of a PhD. The initial focus is on installing an ASOR at each resuscitation bed, with dedicated hardware for each bed (see Appendix page Z; Figure 24: Equipment used for the ASOR version 2, and how it is interconnected). This is done partially because of the state of the current data acquisition system and partially because of the hardware demand that the ASOR places on the system. But also to make the resuscitation beds function as individual units again. This is beneficial for two reasons; firstly because they are occasionally moved to other locations and secondly to maximize stability of the system. The actual testing of the ASOR and collecting patient data to prove its functionality is the biggest time consumer. Because of the effort and time involved in testing, it is worthwhile to invest in equipment, in order to increase testing capacity and obtain the maximum amount of data/experience.

The new systems should be chosen with future expansions in mind. With the availability of pressure and flow measurement, the SpO_2 advisory system can be improved and tested. Additional software will need to be developed to assess and advise on the ventilation part of the resuscitation, i.e. warn for mask leaks.

Interesting will be to discover if advice given by the ASOR will actually improve the control over the SpO_2, and reduce deviation. An unexplored option is the usage of an upper and lower limit during the initial 10 minutes of the resuscitation. A number of experts have suggested such a change [8], and it would clarify the amount of deviation that is acceptable. It could be that by displaying such an acceptable variation, deviation can be further reduced to within that region, or it could be that control is so poor that physicians are unable to stay within the chosen limits. But a large challenge will be proving what the acceptable deviation is.

CONCLUSION

The ASOR, displaying the trends of the various measurements involved in controlling the SpO_2, together with the SpO_2 targets, helped to reduce overexposure to oxygen and high oxygen saturation during the resuscitation of preterm infants. Unfortunately it did not reduce the amount of variation, which is further proof that the control of the SpO_2 is challenging and further technological assistance is needed in order to improve control.

The hypothesis that advice on when and how FiO_2 should be adjusted can be calculated from the current measurements, and that it will improve SpO_2 control remains untested. Although preliminary results are promising, it has become clear that it cannot be tested safely without including pressure and flow measurement, to ensure adequate ventilation. But with those additions implementation of the advisory part of the ASOR should be possible (METC approval has already been obtained). The biggest challenge that remains is validating the advice, to ensure safe operation.

The large variation between preterm infants, their condition and reactions, make judging their needs difficult for clinicians, and provides the developers of an advisory system with similar challenges. A major hurdle is how much is still unknown when it comes to preterm infants; how do they adapt to the transition from intra uterine to extra uterine life, how much exposure to oxygen is dangerous, and how quickly does these damaging effects set in. These uncertainties make that not only the reactions of preterm infants are not fully understood, it also means that the targets and method of controlling are uncertain. By further researching the resuscitation of preterm infants, and collecting more data, more knowledge can be obtained, and technological improvements will aid with better observations and reducing deviation and variation. All of which will hopefully lead to a better understanding, clearer and stricter guidelines and in the end a better start for preterm infants.

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Appendix

TABLE OF CONTEXT OF THE APPENDIX

A.1 ERC GUIDELINES FLOWCHART FOR RESUSCITATION

Newborn Life Support

Dry the baby
Remove any wet towels and cover
Start the clock or note the time

Birth

Assess (tone),
breathing and heart rate

30 sec

If gasping or not breathing
Open the airway
Give 5 inflation breaths
Consider SpO2 monitoring

60 sec

Re-assess
If no increase in heart rate
Look for chest movement

If chest not moving
Recheck head position
Consider two-person airway control
or other airway manoeuvres
Repeat inflation breaths
Consider SpO2 monitoring
Look for a response

Acceptable*
pre-ductal SpO2

2 min : 60%
3 min : 70%
4 min : 80%
5 min : 85%
10 min : 90%

If no increase in heart rate
Look for chest movement

When the chest is moving
If the heart rate is not detectable or slow (< 60)
Start chest compressions
3 compressions to each breath

Reassess heart rate
every 30 seconds
If the heart rate is not detectable or slow (< 60)
Consider venous access and drugs

AT ALL STAGES ASK: DO YOU NEED HELP?

* www.pediatrics.org/cgi/doi/10.1542/peds.2009-1510

Figure 15: Newborn life support algorithm, ERC 2010.

A.2 THE INITIAL FRACTION OF INSPIRED OXYGEN DURING RESUSCITATION

In 2010, all resuscitation councils changed their advice on the initial FiO_2 for resuscitation from 100% oxygen [1-3] to room air [4-6].

Only seven small studies [7-13] with a total of 464 patients, studied resuscitation of very preterm infants with lower oxygen concentrations. The outcomes were evaluated for short-term effects, and none of these trials were set up to evaluate the important longer term outcomes, the most important of which is survival without significant neuro-developmental disability [14].

These seven studies were conducted prior to introduction of the SpO_2 targets and thus all use different targets. Figure 16 shows there was a large spread in both the final SpO_2 level and the time in which these levels should be obtained between the different studies. The method chosen to adjust the FiO_2 after the initial level, was the biggest influence on the outcome of these seven studies. If titration according to SpO_2 was used, starting with a lower FiO_2 had a positive result. Even if FiO_2 is titrated according to SpO_2 levels, the resulting SpO_2 levels depend highly on the initial FiO_2 of 21% or 100% (Figure 17). Between the groups starting with 30% or 90% oxygen this difference is a lot less clear.
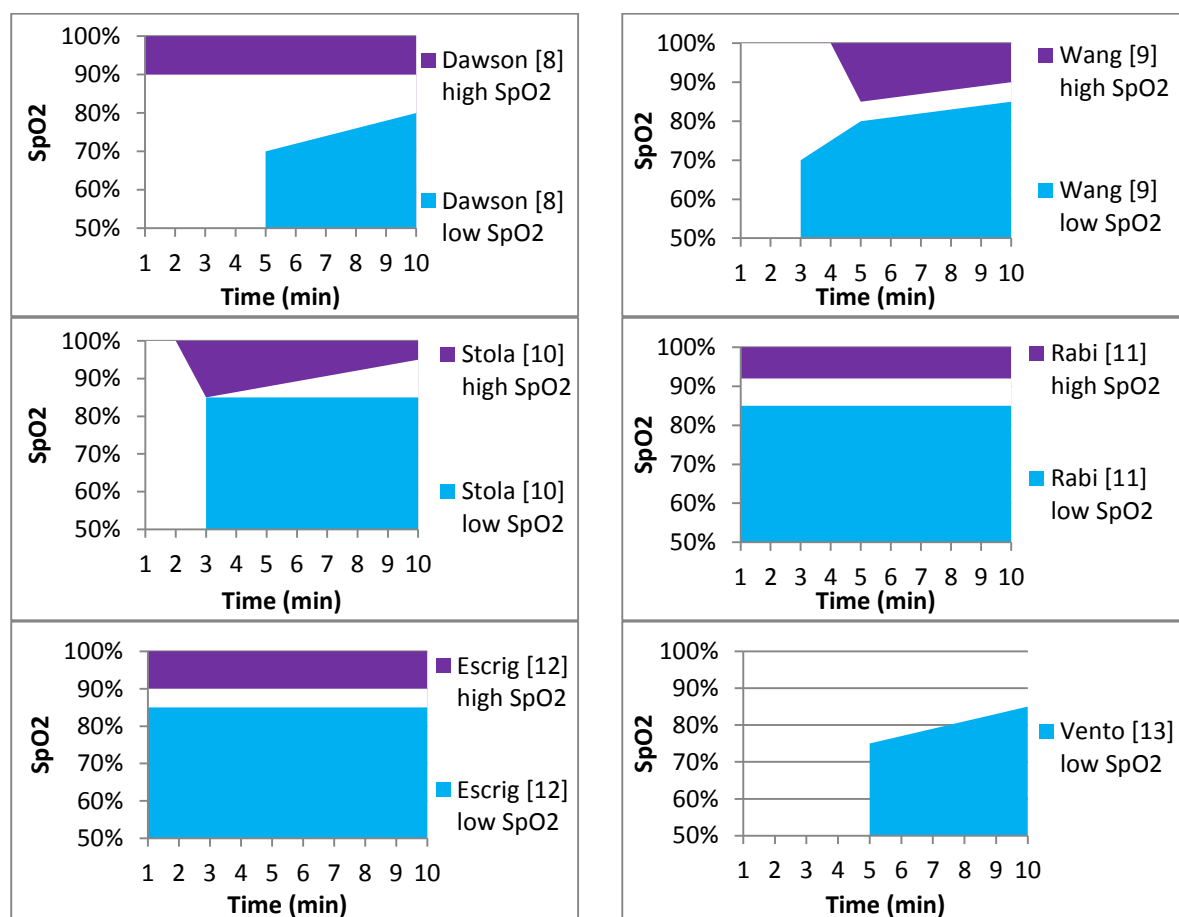
Figure 16: SpO₂ target / upper and lower alarm levels used in 6 of the pilot studies concerning FiO₂ administered to preterm infants.
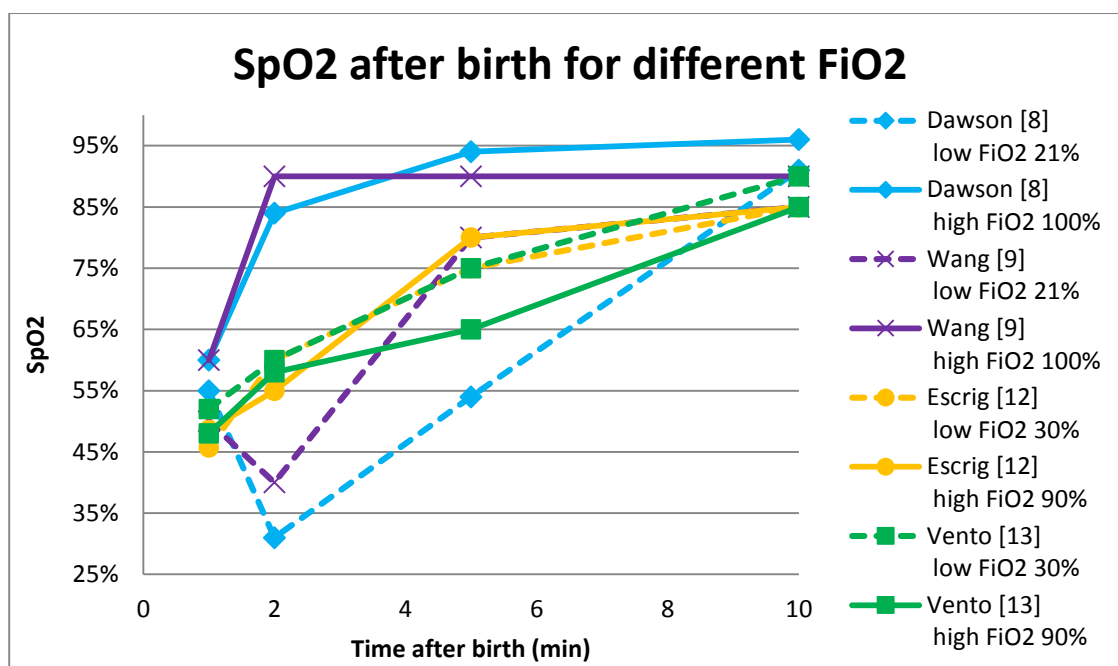
**Figure 17: SpO₂ measurements of the first 10 minutes after birth for high and low initial FiO₂.
Results from the pilot studies concerning FiO₂ administered to preterm infants. In all cases, except Dawson's high FiO₂ of 100%, the FiO₂ was titrated according to the SpO₂ targets seen in Figure 16.**

Currently, a double blinded, randomized study on the optimal FiO₂ to start resuscitation of preterm infants, is being performed at the Erasmus Medical Centre (Rotterdam, the Netherlands). Preterm infants below 32 weeks GA are resuscitated with a starting FiO₂ of either 30 or 65%. The FiO₂ is maintained until the physician intervenes, after which it is titrated according to SpO₂. This study will also look at the long term neuro-development. But how to subsequently adjust the FiO₂ during resuscitation is still unknown, and left to the caregiver to decide.

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A.3   HUMAN CONTROL THEORY

Manual control

The difficulties connected to manual adjustment of the FiO_2 are largely due to either the type of measurement (pulse oximetry), or the unknown state of the infant. A lot of time and effort is invested in improving pulse oximeters, especially with the aid of signal processing [1, 2]. These developments will improve the measurements and subsequently the SpO_2 control. However, there are other ways to improve the control of SpO_2.

Currently, there are 4 measurements involved in the control of SpO_2, each displayed on a different device, in a different location.

- Time after birth
- Target SpO_2
- SpO_2
- FiO_2

With the current devises this means that the physician needs to take his eyes of the infant, and check each measurement individually. During the first minutes of resuscitation the control is more difficult, because the targets form a gradual rise. The physician needs to check the time, interpolate between target values, and keep track of the rate of change between the current SpO_2 and the target. This is a significant mental load that will be reduced by the ASOR, because the trends are displayed in a graph. (See Appendix page F: "Human control theory for more on mental load and performance")

The human as controller

In a review of the literature in the field of human-machine systems, Stassen et al. [3] drew conclusions from linear system theory [4, 5] and optimal filter theory [6]; "...for the correct supervision of a plant; the human supervisor has to be familiar with the plant; that is, he has to possess an Internal representation of:

- The statics and dynamics of the plant to be supervised.
- The tasks to be executed.
- The statistics of the disturbances to be compensated.

Without such an internal representation one cannot count on a human supervisor to act in an optimal way."

Stassen et al. [3] describe the design of an interface as followed; "In formulating the design of a human-machine interface (HUMIF) as an optimization problem, one may state that the optimal HUMIF is the interface that yields the best performance and that imposes a task demand load on the operator that he will experience as that mental load that corresponds with the Willing-To-Spend-Capacity [7] of his mental resources." Where it is important to note that they were looking for a preferred mental load, not a minimal mental load. For an interface used during resuscitation it is important to take into account that the control of the SpO_2 is multifaceted, and not the sole task of the physician. So, during resuscitation the mental load of the interface should be as small as possible.

With experience physicians have learned what to expect, and learned the possible and likely responses of an infant to their actions. With this obtained knowledge a physician can either increase his performance or decrease his mental load, or both. In fact, three possible operators can be characterized [3], i.e.:

- The Wise Supervisor: He uses his knowledge firstly to decrease his mental load to the level of his willing-to-spend-capacity, then he tries to improve his performance.
- The Lazy Supervisor: He will continue to perform at a low level, using his improved knowledge just to decrease his mental load.
- The Ambitious Supervisor: He will focus entirely on his performance, neglecting the fact that he is still operating at a level of mental load that is far above his real willing-to-spend-capacity.

If we look at the manual control of SpO_2 we conclude that the physician can never act in an optimal way, because the exact condition of the infant is unknown. Even if the exact response of the infant was known, a human would still have trouble controlling the SpO_2 because of the dynamics involved.

Human behaviour

Human performance models can be categorized according to their level, Rasmussen [8] distinguishes a Target Oriented Skill-Based Behaviour (SBB); a Procedure Oriented Rule-Based Behaviour (RBB); and a Goal Controlled Knowledge-Based Behaviour (KBB) (Figure 18).
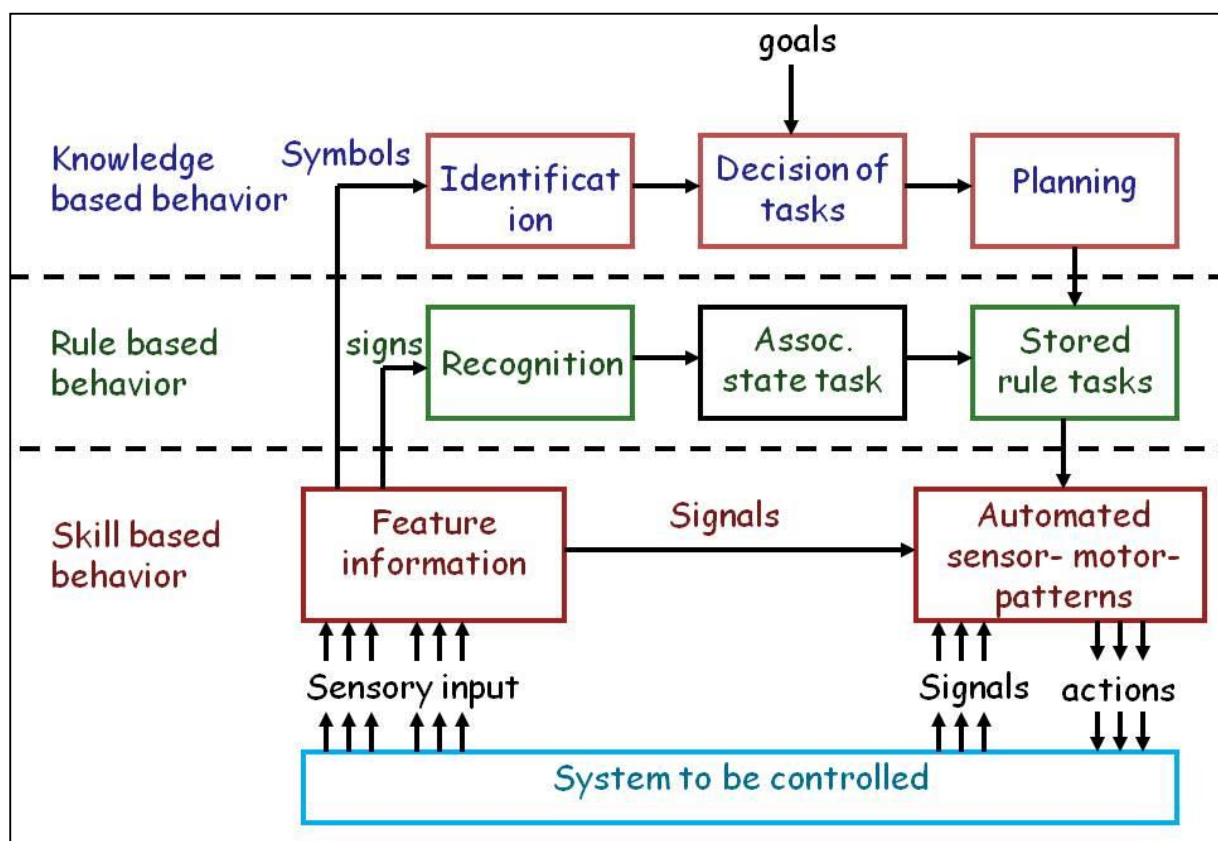
Figure 18: Skill-, Rule- and Knowledge-Based Behaviour [8].
Adapted from Man-Machine Systems, 2009, Prof. P. A. Wieringa, Delft University of Technology, the Netherlands.

At the SBB-level many human performance models have been developed, mainly for manual control and detection tasks. Famous control models, such as the Describing Function Model [9], and the Optimal Control Model [10] have proven their value in the design of controls and displays [11]. The main applications have been to the manual -control of linear, single-input-single-output, relatively rapidly responding systems.

However, from the modelling point of view, the operator's behaviour might show a more important characteristic. In supervisory control, the overall task consists of a number of sub tasks; such as monitoring, interpreting, teaching, whereas in manual control just direct closed loop actions are involved. Hence, the supervisory task is more globally defined, leaving the operator a lot of freedom to choose his own strategy in reaching the goal. Tasks to be performed at the KBB-level require the operator's creativity and intelligence, hence modelling KBB sounds contradictory [3].

Mental load reduction and performance increase; Guidelines and ASOR

Symptom-based emergency operating procedures are intended to be rule-based, to ensure quick response, even though the physician does not understand the true nature of the disturbance. This is an attempt to reduce knowledge-based behaviour (KBB) to rule-based behaviour (RBB) [3]. (See Appendix page H: "Human behaviour for more information on different behaviour classes") The flowcharts as made by the different resuscitation councils (e.g. Appendix page C: Figure 15: Newborn life support algorithm, ERC 2010) , are meant to reduce the KBB task of resuscitating an infant to a RBB task.

Resuscitation as a whole is a supervisory task, of which the manual control of the SpO_2 is just a part and should ideally be a simple skill-based behaviour (SBB) level task. But due to the non-linearity (uncertainties about the needed amount of oxygen, and PaO_2 to SpO_2 relation), the time delay after changes, and the sudden loss of oxygen saturation in the blood, it is not.
In order to control a second order system, a controller requires information about the error and the velocity. For higher order systems information about the acceleration and higher derivatives will be required [12].

The plotting of the target SpO_2 and the measured SpO_2 together in one graph provides the physician with visual information on the error, speed and acceleration of the error. This reduces the order of the control problem, and should increasing its controllability and reduce the mental load that is needed for achieving the same performance [12]. The reduction in mental load can then be used to either reduce the overall mental load to below the willing-to-spend-capacity, or to increase performance [3].

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A.4   INTERVIEWS WITH CLINICAL STAFF

As part of the development of the ASOR, interviews were conducted amongst the clinical staff of the Department of Neonatology of the Erasmus Medical Centre (Rotterdam, the Netherlands). The interviews were conducted to obtain insight into current resuscitation practice, and focused on considerations and tactics for oxygen therapy, monitoring, alarms, annoyances, and possible improvements. The complete interview can be found in Appendix page N: "Interview conducted with the neonatal staff at Erasmus Medical Centre (in Dutch)". Depending on the conversation, additional questions may have been asked to clarify or expand on an answer.

In total 10 clinicians were interviewed, consisting of 6 neonatologists, 1 neonatal fellow, and 3 resident physicians. Although differently phrased, the consensus is that resuscitation is the stable transition from intra-uterine to extra-uterine, with as little intervention as necessary.

Challenges

Most of the interviewed clinicians indicate that either adequate ventilation or the control of SpO_2 is the main challenge during the resuscitation of preterm infants (Figure 19). Only one neonatologist mentioned intubation as one of the biggest challenges.

Main challenges during resuscitation

(Bar chart. Y-axis from 0 to 6. Ventilation: 5, Oxygen therapy: 4, Resist the urge to intervene: 2, Intubation: 1)
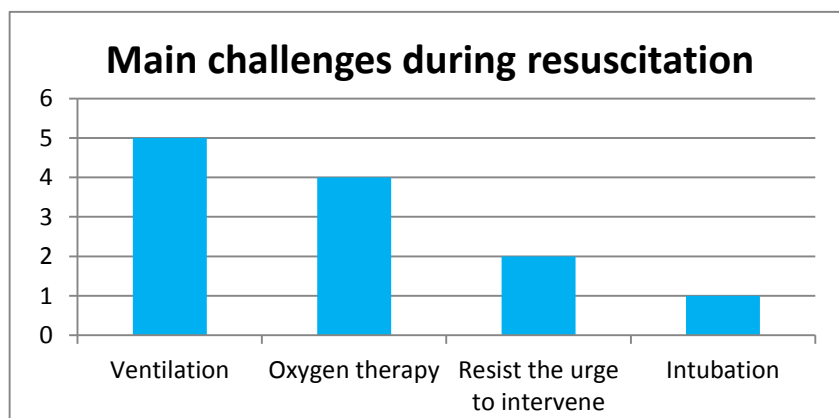
Figure 19: The main challenges during resuscitation of preterm infants, as indicated by the interviewed experts at Erasmus Medical Centre (Rotterdam, the Netherlands).

Information received prior to the resuscitation is often limited; this is partially because of the acute setting, but also because of the suboptimal communication between the obstetrics and neonatology department.

The sensitivity and time to obtain a saturation measurement is the main annoyance among the interviewed specialists of the Erasmus Medical Centre. Most think this will improve with the new pulse oximeters (In the Erasmus MC, the current Nellcor OxiMax N-600x (Covidien-Nellcor, Boulder, USA) pulse oximeter will be replaced by Masimo Rad-87 (Masimo Corporation, Irvine, USA)), but are aware that it will remain a problem. Other annoyances are that laryngoscopes never seem to have the right size, the amount of unnecessary alarms and the lack of space in the resuscitation area.

Ventilation

There are two devices available to tackle one of the main challenges, adequate ventilation. The current standard is the Neopuff t-piece resuscitator (Fisher & Paykel Healthcare, East Tamaki, New Zealand), which has the benefit of preset pressure limits for both positive end expiratory pressure (PEEP) and peak inspiratory pressure (PIP). The other option is the older Jackson Rees modification T-piece system breathing system (Intersurgical, Wokingham, United Kingdom), where manual closing of the exit of an elastic bag determines the pressure.

All interviewees acknowledged that the use of the Jackson Rees is riskier than the use of the Neopuff, because of the added risk of using too high pressures. But those who were trained with the Jackson Reese indicated that they prefer the Jackson Rees for dealing with difficulties of lung inflation, because they find it much easier to quickly give higher PEEP and or PIP pressure with the Jackson Rees. The clinicians that switch to the Jackson Reese when lungs are difficult to inflate, do not switch back ones they have found a stable PEEP level. The more senior staff uses the Jackson Rees exclusively, either because they are used to it, like the ease of adjustment, or because they are better able to maintain a leak free connection between mask and infant.

Oxygen therapy

After proper ventilation is established, the second main challenge is oxygen administration. The fraction of inspired oxygen (FiO_2) is adjusted depending on the blood oxygen saturation, measured by pulse oximetry(SpO_2).

With infants born without complications and with a gestational age (GA) above 30 weeks, oxygen therapy is started at 21% by all interviewed experts. Below 30 weeks GA, clinicians of the Erasmus Medical Centre start with either 21% or 30%, where both percentages were claimed to be the institutions standard. Other than the initial FiO_2 and the plastic bag for temperature control, there are no real differences based on the gestational age in the approach of a resuscitation. As one neonatologist stated; "The higher expected need of extremely premature infants for respiratory support is offset by their higher sensitivity to over exposure to oxygen".

The SpO_2 targets introduced in the new guidelines (ERC 2010 [1]) have caused most of the interviewed specialists to be more reserved in increasing FiO_2, and they now allow the saturation more time to rise on its own. All interviewed clinicians indicated to follow the targets, but in varying degrees of accuracy, from ±5% to 'as long as the trend is similar'. FiO_2 is only adjusted after a SpO_2 measurement is obtained, or when the heart rate fails to rise. FiO_2 is normally adjusted with step sizes between 5 and 10%, or bigger if the response after the initial increase is very slow. During reanimation, i.e. persistent HR < 60 bpm, the FiO_2 is turned to 100% straight away.

Alarms

A big problem in NICU's are unnecessary alarms, resulting in reduced attention to the alarms and excessive noise pollution. In the resuscitation room, alarms are quickly turned off, reducing the noise pollution, but not the annoyance.

The current alarms of the pulse oximeter are set to the NICU levels (SpO_2 between 85 – 93%, pulse rate<100). These settings result in a large number of false alarms during the first 10 minutes of resuscitation. Most of the interviewed said they ignore the alarms completely, and the majority indicated that they don't need an alarm during that period, because they are so focused on the task anyway. An alarm for the more stable period at the end of resuscitation would be appreciated by most, because then there is a chance they are focusing on other tasks and might miss a problem. A difference in the type of alarm and the loudness depending on severity and time passed would also help reduce the nuisance during resuscitation.

ASOR

All interviewed clinicians thinks that a new monitor, that combines the measured parameters on a single screen, could be an improvement, although some are critical on how easy it will be to read a graph. There was a mixed response to whether the display of the pulse rate in the graph would be beneficial or not. Because the heart rate only needs to be above a certain threshold, close observation was deemed unnecessary by some. Another concern is the familiarity with the current setup, and the time it will take to get used to a new one.

The new monitor should be similar to other monitors used in the hospital when it comes to layout and use of colour. Most interviewed clinicians don't have a strong association between a measured variable and a colour, but blue for SpO_2 and red for heart rate were mentioned most often. The current monitors used in the NICU are green monochromatic screens, but they will be replaced by new monitors by Dräger (Lübeck, Germany) with different colours and layout. The monitor on the transport incubator is made by Philips Healthcare (Eindhoven, The Netherlands) and will most likely not be replaced in the near future.

A reminder when it is time to take the APGAR score would be appreciated by most. And some interviewed clinicians would like to be able to hear the heart rate and saturation (hart rate as frequency, saturation as pitch) during the initial rise, and during procedures such as intubating. This would allow them to keep their eyes on the infant and the task at hand.

Most interviewed clinicians are reluctant about receiving advice from a machine on when and how to adjust the FiO_2. The machine would need to prove itself, and the manner in which the advice is given should not be too obtrusive. Advice contradicting with procedures (like increasing FiO_2 while attempting to intubate) would be very annoying. Medical complications would be the main reason to diverge from advice given by a machine.

Further additions

Tidal volumes, PEEP and PIP pressures, CO_2, NIRS, EEG, blood pressure, and temperature were suggested as additional measurements that could help improve the resuscitation of preterm infants. Not necessarily as a continuously displayed measurement, but just during certain procedures (intubation), for research or as an alarm indicator. Most of the interviewed clinicians indicated that they want the resuscitations to be recorded in order to view, asses, and discuss the performance of the team afterwards. Currently, resuscitations are not discussed afterwards, nor do the neonatologist ever observe how their colleagues tackle challenges.

References

1.   European_Resuscitation_Council, *European Resuscitation Council Guidelines for Resuscitation 2010*. 2010, Elsevier: Resuscitation.

Interview conducted with the neonatal staff at Erasmus Medical Centre (in Dutch)

Voor mijn afstuderen wil ik met technische middelen de opvang verbeteren.

Kunt u mij kort vertellen wat voor u de opvang van een neonaat inhoud? (welke stappen, hoe lang duurt het)

Zijn er verschillen in handelen voor (extreme) prematuren?

Op welke manieren verkrijgt u informatie over de patiënt voor/tijdens de opvang?

Wat zijn voor u de grootste uitdagingen tijdens de opvang?

Zou u de opvang willen veranderen? Wat zou u dan anders willen zien?

Zou de opvang door technische ondersteuning verbeterd kunnen worden? Zo ja, heeft u ideeën hoe?

Ergert u zich aan bepaalde apparaten / handelingen tijdens de opvang?

Met de nieuwe richtlijnen voor de opvang van pasgeborenen zijn er ook zuurstof saturatie doelen voor tijdens de opvang ingesteld.

Hecht u belang aan richtlijnen tijdens de opvang?

Weet u wat de huidige richtlijnen voor de streefwaarden van de saturatie/hartslag/etc. zijn?

Hoe nauwkeurig volgt u de richtlijnen? (kunt u aangeven hoeveel afwijking in saturatie of tijd u acceptabel vindt)

Met welk percentage zuurstof begint u, als blijkt dat een prematuur extra zuurstof nodig heeft? (buiten de huidige zuurstof studie)

Het is mogelijk om de verschillende metingen gecombineerd op een monitor weer te geven.

Verwacht u dat een dergelijke monitor iets de opvang verbeterd?

Welke variabelen zouden op deze monitor af te lezen moeten zijn?

Hoe zou u de variabelen het liefst weergegeven zien?

Wanneer parameters in een grafiek worden getoond is het mogelijk om de ontwikkeling van trends te zien.

Voor welke variabelen zou u dit als een voordeel zien?

Wilt u deze dan samen in één enkele grafiek zien, of iedere variabele in een aparte grafiek?

Als bijvoorbeeld de SpO_2 weergegeven word in een grafiek, zou u de waarde dan ook numeriek willen zien?

N

Geldt dat voor alle variabelen die u in een grafiek zou willen zien? (welke ook numeriek)

Hoe lang zou de tijdschaal van een grafiek moeten zijn? (hoe ver zou u terug in de tijd willen kijken naar hoe de variabelen zich ontwikkelen?)

Kunt u voor de volgende variabelen aangeven met welke kleur u deze associeert?
SpO_2
SpO_2 richtlijnen
Hartslag
FiO_2
CO_2
Tijd na de bevalling (apgar tijd)

Het is technisch mogelijk om een advies te geven over de FiO_2 die toegediend zou moeten worden. b.v. aan de hand van de SpO_2, tijd, hartslag en huidige FiO_2

Zou u het nuttig vinden als een dergelijk advies gegeven zou worden?

Wanneer zou u dit advies wel/niet overnemen in uw handelingen?

Hoe vaak zou u advies willen krijgen over de hoeveelheid toe te dienen zuurstof? (hoe vaak mag dit advies wisselen?)

Wat voor type bediening voor simpele handelingen heeft uw voorkeur?
(start / stop / reset / invoeren van een variabele zoals gewicht)
Toetsenbord / Muis
Touchscreen
Tiptoetsen
Draai knoppen
Apple controller (combinatie van draai en druk knop)

Alarm

Kunt u nu, wanneer er een alarm afgaat en alleen hoort, zeggen met welk apparaat er iets aan de hand is en wat er is? (niet alleen tijdens de opvang, maar in het algemeen)

In een ideale situatie welke variabelen zouden tijdens de opvang een onderscheidend alarm moeten hebben? (audio en/of visueel)

Wat voor type alarm vind u prettig?

A.5   THE WORKING OF THE ASOR
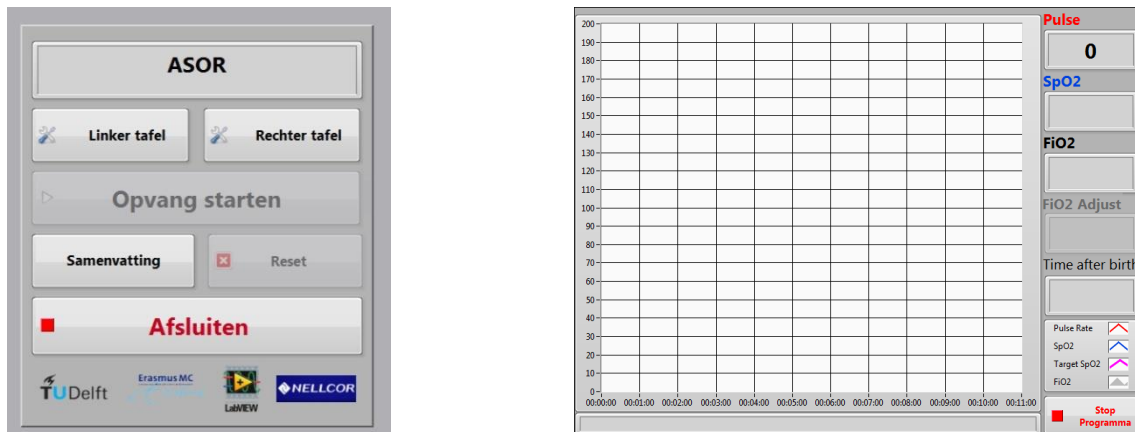
Figure 20: Start up screen (left) and main screen (right) of the ASOR.

User must select the appropriate resuscitation table (patient data), after which the green indicator turns on, and the resuscitation can be started. Otherwise an error is displayed prompting the user to input the necessary data, or giving the option to simulate a resuscitation. After the resuscitation, a summary can be viewed (samenvatting), showing a graph of the entire resuscitation. With the reset button the ASOR is reset, and ready for the next resuscitation. All data is stored on the internal hard drive.

Table 1 is a list of the sub programs that make up the ASOR, and Figure 21 shows how they are interconnected. A detailed working of the mean ASOR can be seen in Figure 22, which shows the graphical program of Readout_800_600V1.vi.

Table 11: List of SubVi's that make up the ASOR.

UserInputV2.vi

Readout_800_600_V1.vi

SpO2FaultCheck.vi

ErrorMsgFiO2.vi

ErrorMsgSpO2.vi

ErrorMsg.vi

TargetSpO2.vi

PrebForGraph.vi

Scale_Graph.vi

Summary.vi

Simulate_800.vi

TargetSpO2.vi

PrebForGraphA.vi

SimulatieGraph 2 (SubVI).vi

Scale_Graph.vi

SimulationVariables.vi

Variables.vi
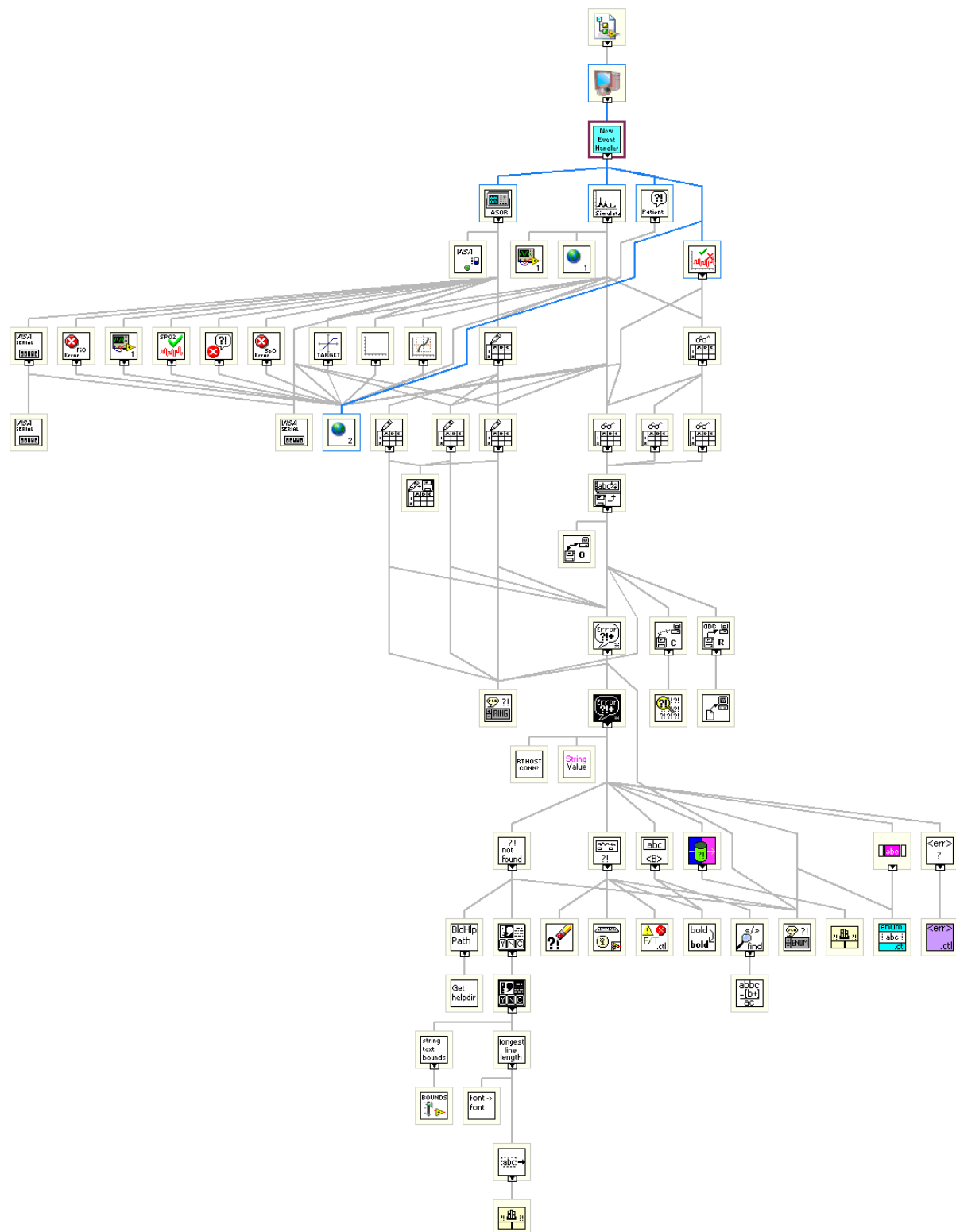
Figure 21: Position in Hierarchy of the Vi's that make up the ASOR.
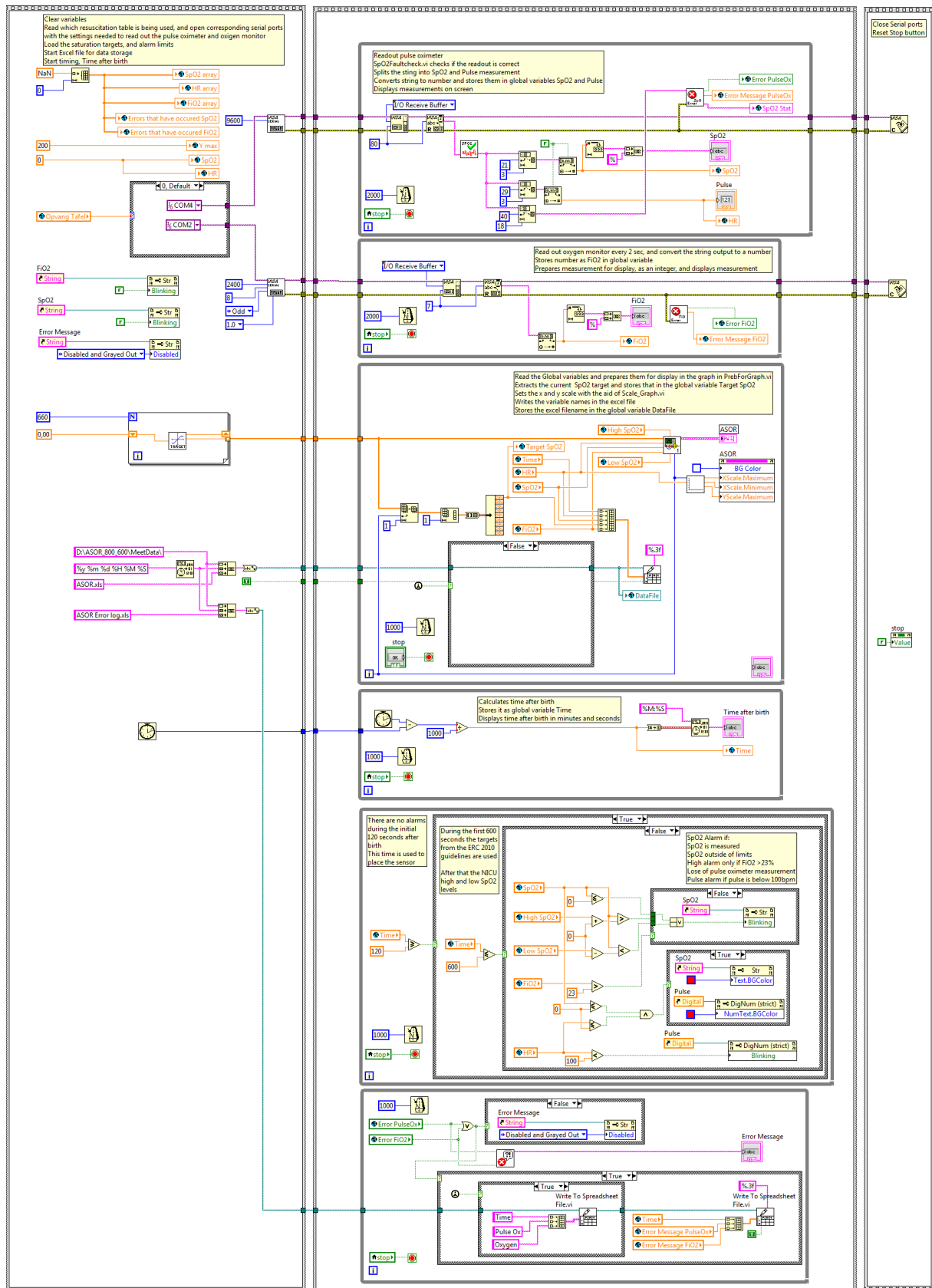
Figure 22: Overview of the main control loop of the ASOR, as programmed in LabView.

Advise Module

Table 12: The structure, rules and corresponding actions of the advice module of the ASOR, based on proportional control.
The table describes the rules that are used each loop (every second) to determine if and how the FiO2 should be adjusted. A field that is filled black is enabled, a field that is filled grey is disabled.

Time after birth (s)	Condition	Action — Alarm: No pulse oximetry	Pulse rate	SpO2	Predicted SpO2	FiO2	FiO2 Adjustment	Description
Always	Calculate	Avg SpO2						
		Avg Speed of Avg SpO2						
		Acc of Avg SpO2						
		Speed Target						
		Check if Speed of SpO2 is in bounds (not used)						
0 - 120	No alarms	(grey)	(grey)	(grey)	(grey)	(grey)		During the first 2 min no alarms are triggered and no advice is given
	No advice						(grey)	
120 - ∞	If SpO2 and Pulse rate = 0	(black)	(grey)	(grey)	(grey)	(grey)	(grey)	Alarm for no data from the pulse oximeter
	IF 0 < Pulse rate < 100	(grey)	(black)	(grey)	(grey)	(grey)	100	Pulse rate below threshold, FiO2 to max
	IF FiO2 < 95	(grey)	(black)	(grey)	(grey)	(black)		

Time	Condition				Action — Alarm					FiO2 Adjustment	Description
					No pulse oximetry	Pulse rate	SpO2	Predicted SpO2	FiO2		
120 - 600	IF SpO2 is within Target +/- 5 range AND Pred. SpO2 within Pred Range +/- 5				(gray)	(gray)	(gray)	(gray)	(gray)	(gray)	SpO2 on target and predicted to remain on target.
	ELSE	IF SpO2 is outside Target +/- 5 range					■				
		IF |SpO2 -Avg SpO2| ≥ 10 OR FiO2 is adjusted by +/- 2 OR SpO2 = 0			No advice possible					(gray)	Avg not close to measured value OR Time out due to FiO2 adjustment or lose of SpO2 signal
			IF Pred. SpO2 is out of Pred. Target range					■			SpO2 is predicted to go off target
		ELSE	IF Avg SpO2 - Target + 5 > 0 AND Pred. SpO2 - Pred. Target SpO2 + 5 > 0 AND Speed SpO2 ≥ (Speed Target / 1,2)						■	Avg SpO2 - Target + 5	SpO2 and predicted SpO2 are above the target, and the speed is larger than the target speed
			IF Avg SpO2 - Target - 5 < 0 AND Pred. SpO2 - Pred. Target SpO2 - 5 < 0 AND Speed SpO2 ≤ (Speed Target * 1,2)						■	Avg SpO2 - Target - 5	SpO2 and predicted SpO2 are below the target, and the speed is smaller than the target speed
			IF Avg SpO2 - Target + 5 > 0 AND Pred. SpO2 - Pred. Target SpO2 - 5 < 0						■	Pred. SpO2 - Pred Target - 5	SpO2 is above the target but is predicted to shoot through the target range
			IF Avg SpO2 - Target - 5 < 0 AND Pred. SpO2 - Pred. Target SpO2 + 5 > 0						■		SpO2 is below the target but is predicted to shoot through the target range
				IF Speed SpO2 ≥ (Speed Target / 2,5)						10	Speed is so high a big overshoot is likely
				ELSE						Pred. SpO2 - Pred Target + 5	
			ELSE						(gray)	0	No adjustment, SpO2 is moving towards the target
			IF Pred. SpO2 - Pred Target + 5 > 0 AND Speed SpO2 ≥ (Speed Target / 1,2)					■			
			IF Pred. SpO2 - Pred Target - 5 < 0 AND Speed SpO2 ≤ (Speed Target * 1,2)					■			

Time	Condition				No pulse oximetry	Pulse rate	SpO2	Predicted SpO2	FiO2	FiO2 Adjustment	Description
600 - ∞	IF SpO2 is within Target range AND Pred. SpO2 within Pred Range										SpO2 on target and predicted to remain on target.
	ELSE	IF SpO2 is outside Target range					■				
		IF |SpO2 -Avg SpO2| ≥ 10 OR FiO2 is adjusted by +/- 2 OR SpO2 = 0			No advice possible						Avg not close to measured value OR Time out due to FiO2 adjustment or lose of SpO2 signal
		IF Pred. SpO2 is out of Pred. Target range						■			SpO2 is predicted to go off target
		ELSE	IF Avg SpO2 - High Target > 0 AND Pred. SpO2 - High Target> 0						■		SpO2 and predicted SpO2 are above the target, and the speed is larger than the target speed
				IF (Pred. SpO2 - High Target / 2) > Avg SpO2 - High Target						(Pred. SpO2 - High Target) / 2	
				ELSE						Pred. SpO2 - High Target	
			IF Avg SpO2 - Low Target < 0 AND Pred. SpO2 - Low Target < 0						■		SpO2 and predicted SpO2 are below the target, and the speed is smaller than the target speed
				IF (Pred. SpO2 - Low Target / 2) > Avg SpO2 - Low Target						(Pred. SpO2 - Low Target) / 2	
				ELSE						Pred. SpO2 - Low Target	
			IF Avg SpO2 - High Target > 0 AND Pred. SpO2 - Low Target < 0							■	Pred. SpO2 - Low Target	SpO2 is above the target but is predicted to shoot through the target range
			IF Avg SpO2 - Low Target < 0 AND Pred. SpO2 - High Target > 0							■	Pred. SpO2 - High Target	SpO2 is below the target but is predicted to shoot through the target range
			ELSE							0	No adjustment, SpO2 is moving towards the target

Time	Condition	Action						Description
		Alarm					FiO2 Adjustment	
		No pulse oximetry	Pulse rate	SpO2	Predicted SpO2	FiO2		
Always	IF $|$FiO2 Adjustment$|$<5	FiO2 step = FiO2 Adjustment x (((5 - $|$FiO2 Adjustment$|$)/5)+1)						Enlarges small FiO2 adjustments (0-5)
	ELSE	FiO2 step = FiO2 Adjustment						
	(((FiO2/20)*0,2)+0,8)=FiO2 correction factor	FiO2 step * FiO2 correction factor						the FiO2 step is scaled dependent on the current FiO2
	IF FiO2 step >5	Rounded of to multiplications of 5						To make larger step sizes more intuitive
	IF -1 < FiO2 step <1	Rounded of to -1 or 1						To ensure small steps don't get rounded of to 0
	ELSE	No action						
	IF FiO2 + FiO2 step > 100	New FiO2 = 100						Limits advised FiO2 between 21 and 100%
	IF FiO2 + FiO2 step < 21	New FiO2 = 21						

Equipment setup
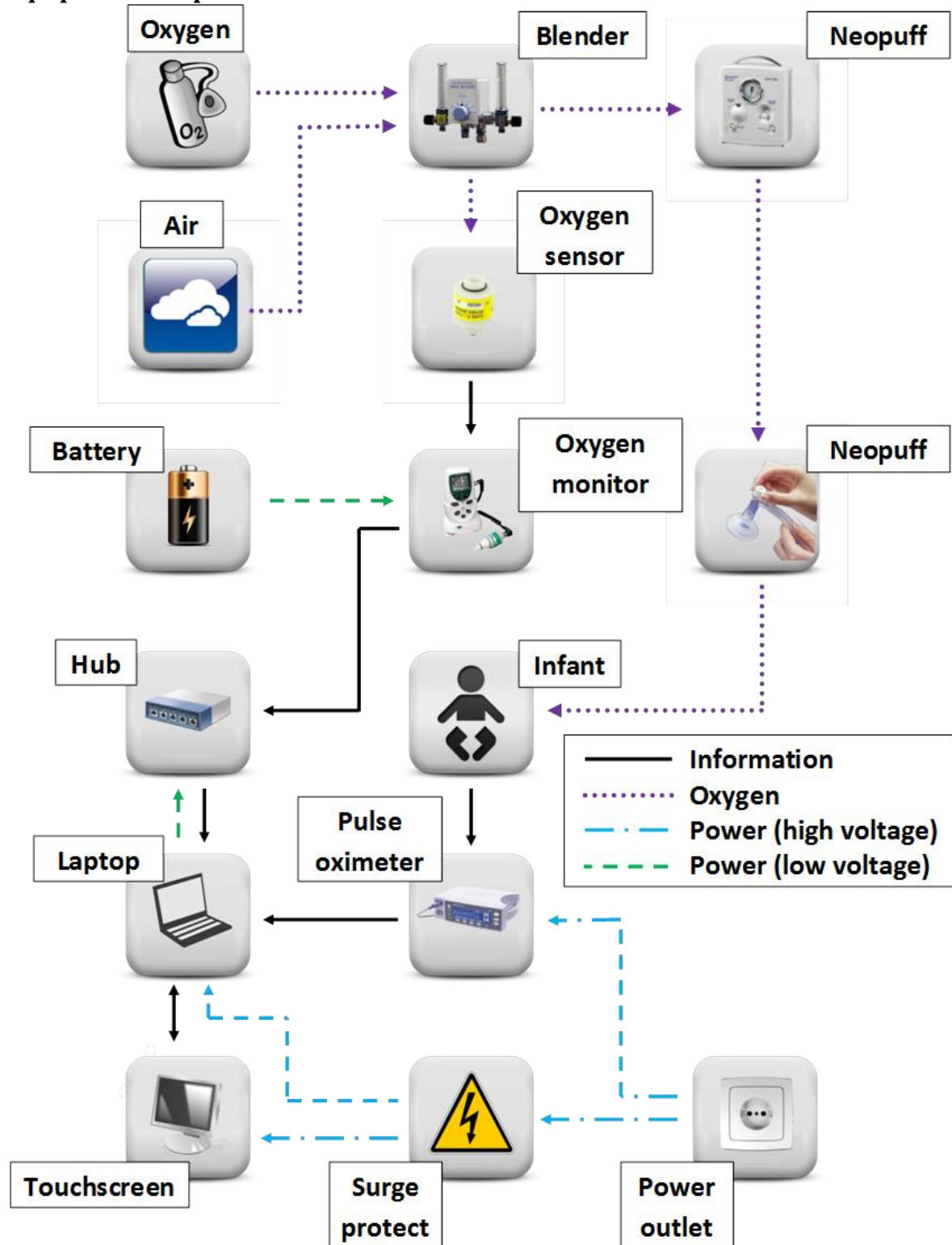
Figure 23: Equipment used for the ASOR version 1, and how it is interconnected.
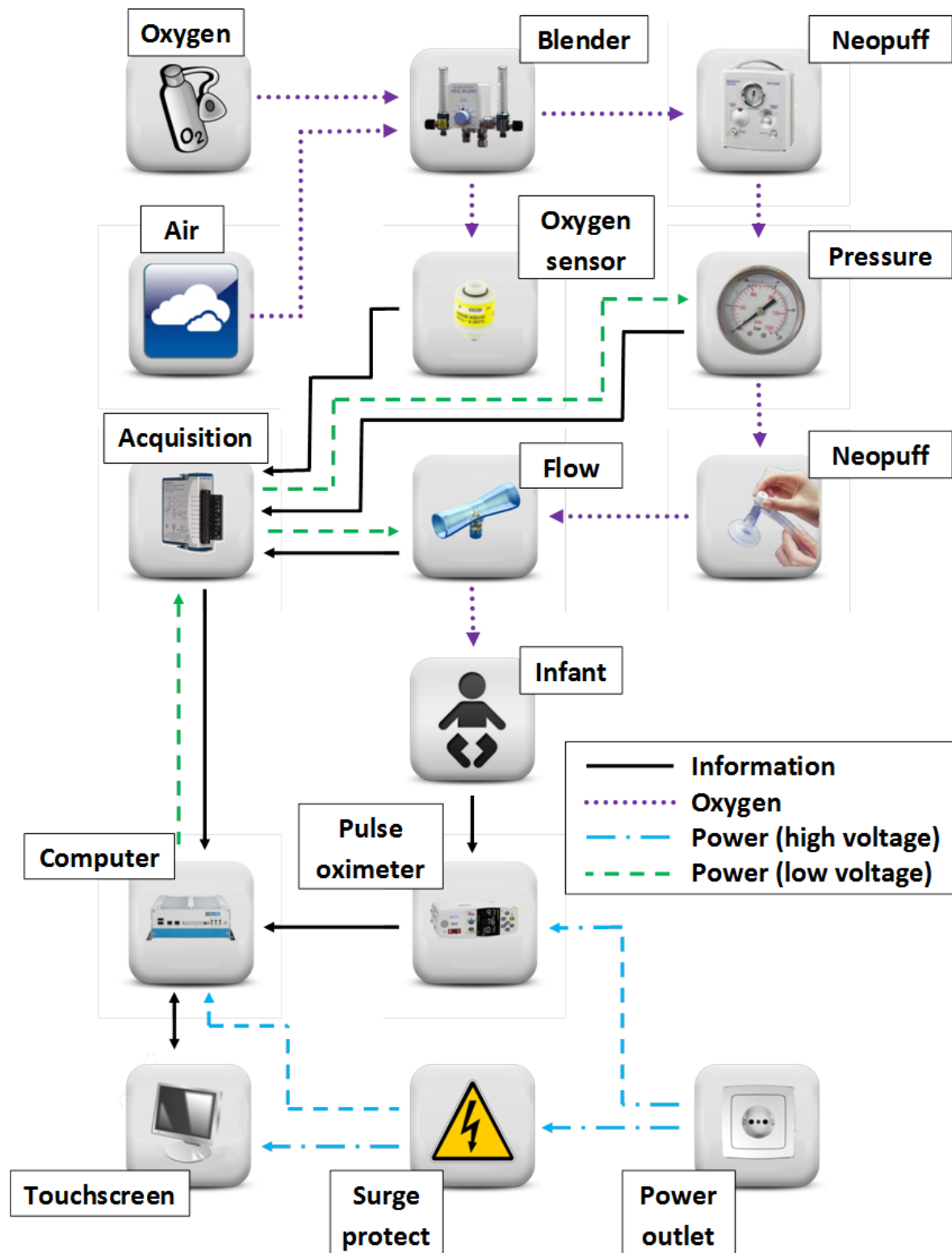
Figure 24: Equipment used for the ASOR version 2, and how it is interconnected.

A.6 QUESTIONNAIRE AFTER RESUSCITATION WITH THE ASOR; USER FEEDBACK (IN DUTCH)

De hoeveelste opvang met ondersteuning van de ASOR was dit voor u?

………

Heeft u tijdens de opvang gebruik gemaakt van de ASOR?

- ○ Ja
- ○ Ja, maar alleen nadat de patiënt stabiel was
- ○ Ja, maar pas na dat ik naar de saturatie monitor gekeken had
- ○ Nee
- ○ Anders, namelijk; ….

Zo ja, vind u dat de ASOR bij gedragen heeft aan het beter volgen dan de saturatie richtlijnen gedurende de eerste 10 minuten?

- ○ Ja
- ○ Nee
- ○ Misschien / weet niet

Heeft de ASOR voor u bijgedragen aan het beter binnen de alarm grenzen blijven na de eerste 10 minuten na geboorte?

- ○ Ja
- ○ Nee
- ○ Misschien / weet niet

Heeft de ASOR voor u bijgedragen aan het beter inschatten van de zuurstof behoefte van de patiënt tijdens deze opvang?

- ○ Ja
- ○ Ja, maar alleen gedurende de eerste 10 minuten
- ○ Ja, maar alleen na de eerste 10 minuten
- ○ Nee
- ○ Misschien / weet niet

Heeft de ASOR voor u bijgedragen aan het gebruik van minder zuurstof tijdens deze opvang?

- ○ Ja
- ○ Ja, maar alleen gedurende de eerste 10 minuten
- ○ Ja, maar alleen na de eerste 10 minuten
- ○ Nee
- ○ Misschien / weet niet

Z.O.Z.

Was voor u de werking van de ASOR vooraf duidelijk?
- ○ Ja
- ○ Ongeveer
- ○ Nee

Is, na deze opvang, u begrip van de ASOR veranderd?
- ○ Ja, namelijk;….
- ○ Nee
- ○ Misschien / weet niet

Hoe zou voor u het gebruik van de ASOR vergroot kunnen worden?
- ○ Het scherm beter positioneren
- ○ Een groter scherm
- ○ Het gebruik van een groter lettertype
- ○ Betere uitleg over de werking
- ○ Gewenning
- ○ Andere kleuren
- ○ Niet
- ○ Anders, namelijk …..

Zijn er (andere) punten die u veranderd zou willen zien aan de ASOR?

…….

Heeft u verder nog op,- of aanmerkingen?

…….

Zou u deze vragenlijst terug willen geven aan Tom, achter willen laten in het postvakje van Denise Rook of af willen geven bij Karin Suvaal (Sp-3433)

Hartelijk dank voor de feedback en dat u de tijd heeft genomen om deze vragenlijst in te vullen,
Tom Goos
Sk-2210
t.goos@erasmusmc.nl
06-41859608

A.7 RISK ANALYSIS

To identify the risks associated with the use of ASOR, a risk analysis (ISO 14971 [1]) in the form of a failure mode and effects analysis (FMEA) was started (ICE 60812 [2]). This FMEA was executed on a component level for the ASOR as a whole, and on a software level for the ASOR version 1 with an addition for the advisory part of version 2. The FMEA tables can be found in the Appendix page EE: Table 15: FMEA of the measurement equipment, Table 16: FMEA of the software of ASOR on page NN, and Table 17: Additional FMEA for the software of the advice given by ASOR version 2 on page RR.

The main risk the ASOR presents is the supply of false or unreliable information. Providing false information to the physician may lead to a suboptimal or incorrect oxygen therapy. The risks associated with a system failure are less because the ASOR runs parallel with the existing equipment. In case of failure the test setup is such that the original equipment can be used, the original layout is not changed, and the additional ASOR screen does not block the view.

To prevent that false information is displayed or used for the calculation of advise, the ASOR software incorporates a number of checks to check whether the equipment is connected properly (input string), and whether the measurements are within the expected range ($0 \leq$ pulse rate ≤ 250, $0\% \leq SpO_2 \leq 100\%$, $21\% \leq FiO_2 \leq 100\%$). The check if the measurements are within the expected range, also incorporates a check to determine if there is a measurement obtained at all. If the measurements are out of range or not obtained, advise is not given, and the appropriate alarm is triggered (see Results: Alarms on page 27 for additional information). These checks are performed within the readout loops, to ensure that all used measurements are correct.

There are some residual risks left in the current version of the ASOR. Most are due to the large number of connections between the different devices, of which some are without fasteners. The failure point can be identified based on the error displayed on the ASOR, so that the error can be resolved. A software module checking all connections before the start of the ASOR would be preferable, because possible failures can be tackled before the resuscitation is started. Another issue is the limited storage space. Although the stored files are small, it can occur that the computer runs out of storage space. A warning before there is too little room left to store at least two hour of data should be given as soon as this occurs, but not during the resuscitation.

During the use of the ASOR, one temporary failure occurred, namely the USB-cable between the laptop and the serial to USB hub got disconnected. An error informing the user of the issue was displayed on the screen after which it could easily be reconnected and the ASOR continued without further issues.

Software development
In accordance to IEC 62304; Medical device software - Software life-cycle processes [3], the ASOR version 1 is class A, because "No injury or damage to health is possible" as a direct result of the use of ASOR version 1. The resulting requirements that must be met are listed in Table 13.

Version 2 of the ASOR, with the added advise on the FiO_2 that should be administered, is of class B, because "Non-serious injury is possible". This risk is due to the fact that if the physician follows incorrect advice given by the ASOR, it can result in a short under or over exposure to oxygen, and a short period of hypo,- or hyperoxia. The result of incorrect oxygen exposure will quickly be visible in the obtained measurement and can be corrected. For class B software the additional requirements according to IEC 62304 [3] are listed in Table 14.

Because the ASOR is still a research device not all requirements from IEC 62304 [3] are met, but they are taken into account as much as possible to make future development into a commercially available system easier.

Table 13: Risk management and software development requirements for class A software.
According to IEC 62304; Medical device software - Software life-cycle processes [3].

Requirement	Description
4.1	Quality management system
4.2	Risk management (ISO 14971)
4.3	Software safety classification
5.1.1	Software development plan
5.1.2	Keep software development plan updated
5.1.3	Software development plan to system design and development
5.1.6	Software verification planning
5.1.7	Software risk management planning
5.1.8	Documentation planning
5.1.9	Software configuration management planning
5.2.1	Define and document software requirements from system requirements
5.2.2	Software requirement content
5.2.4	Re-evaluate medical device risk analysis
5.2.5	Update system requirements
5.2.6	Verify software requirements
5.5.1	Implement each software unit
5.8.4	Document released versions
7.4.1	Analyse changes to medical device software with respect to safety

Table 14: Risk management and software development requirements for class B software.
According to IEC 62304; Medical device software - Software life-cycle processes [3].

Requirement	Description
5.1.5	Software integration and integration planning
5.1.10	Supporting items to be controlled
5.1.11	Software configuration items control before verification
5.3.1	Transform software requirements into an architecture
5.3.2	Develop an architecture for the interfaces of software items
5.3.3	Specify functional and performance requirements of soup item
5.3.4	Specify system hardware and software required by soup item
5.3.6	Verify software architecture
5.4.1	Refine software architecture into software units
5.5.2	Establish software unit verification process
5.5.3	Software unit acceptance criteria
5.5.5	Software unit verification
5.6.1	Integrate software units
5.6.2	Verify software integration
5.6.3	Test integrated software
5.6.4	Integrated testing content

5.6.5	Verify integration test procedures
5.6.6	Conduct regression tests
5.6.7	Integration test record contents
5.7.1	Establish tests for software requirements
5.7.4	Verify software system testing
5.7.5	Software system test record contents
5.8.1	Ensure verification is complete
5.8.2	Document known residual anomalies
5.8.3	Evaluate known residual anomalies
5.8.5	Document how released software was created
5.8.6	Ensure activities and tasks are complete
5.8.7	Archive software
5.8.8	Assure repeatability of software release
7.1.1	Identify software items that could contribute to a hazardous situation
7.1.2	Identify potential causes of contribution to a hazardous situation
7.1.3	Evaluate published soup anomaly lists
7.1.4	Document potential causes
7.1.5	Document sequences of events
7.2.1	Define risk control measures
7.2.2	Risk control measures implemented in software
7.3.1	Verify risk control measures
7.3.2	Document any new sequences of events
7.3.3	Document traceability
7.4.2	Analyse impact of software changes on existing risk control measures
7.4.3	Perform risk management activities based on analyses

References

1. CEN, *Medical devices - Application of risk management to medical devices*. 2007, CEN Management Centre.
2. CENELEC, *Analysis techniques for system reliability - Procedure for failure mode and effects analysis (FMEA)*. 2006, European Committee for Electrotechnical Standardization.
3. IEC, *Medical device software – Software life cycle processes*. 2006, International Electrotechnical Commission.

Table 15: FMEA of the measurement equipment.

1. ID	2. function / oper. status	3. failure mode	4. effect on other parts	5. effect on system	6. measures	7. fail frequency	8. ranking effect	causes / remarks
AC outlet	Provide electricity	No electricity	No power	System fails	Emergency power supply within the Hospital			Net power fails
		Wrong voltage too low	Will not function	System fails	Integrated transformer / instructions for use			If used in different country
		Wrong voltage too high	Fuse blows	System fails	Integrated transformer / instructions for use			If used in different country
Power filter	Filters out harmful power effects to and from the network	Fuse blows	No power	System fails	Surge measurements within the hospital			Problem caused by either computer or touchscreen connected to it
		Fails to filter out effects	Main room fuse will blow, possible fire. Damage to other equipment	System fails	Surge measurements within the hospital			Problem caused by either computer or touchscreen connected to it
	Transport electricity	No conduction	No power to computer or screen	System fails	Replace cord Watch out not to damage it in use			Cord damaged in use
		Not connected	No power to computer or screen	System fails	Connect cord			Cord not plugged in
		Short circuit	Main room fuse will blow, possible fire. Damage to other equipment	System fails Possible damage to power network	Replace cord Surge measurements within the hospital Watch out not to damage it in use			Cord damaged in use

		Trip over / get pulled	No power to computer or screen Pull computer of table	System fails	Place cord out of the way			User interacting with cable
Computer power cord	Transport electricity	No conduction	No power to computer	System fails	Replace cord Watch out not to damage it in use			Cord damaged in use
		Not connected	No power to computer	System fails	Connect cord			Cord not plugged in
		Short circuit	Fuse of power filter will blow.	System fails	Replace cord Watch out not to damage it in use			Cord damaged in use
		Trip over / get pulled	No power to computer Pull computer of table	System fails	Place cord out of the way			User interacting with cable
Computer	Run software	Software crash		System fails				
		Hardware crash	No image on screen	System fails				
		Falling of table	Pull cables or other equipment	System fails	Place stable on table			
	Collect data from sensors	No connection	No input	System fails	Alarm on screen Check connections			
	Send data to screen	No connection	No image on screen	System fails	Check connections			
		Incorrect settings	No image on screen	System fails	Reset settings			
			Distorted image on screen	System fails	Reset settings			
	Receive input from touchscreen	No connection	No user input	System fails	Check connections			

VGA - USB cable	Transport signals between computer and touchscreen	No conduction	No image on screen No user input	System fails	Replace cord Watch out not to damage it in use			Cord damaged in use
		Not connected	No image on screen No user input	System fails	Connect cord			Cord not plugged in
		Short circuit	No image on screen No user input Possible failure of screen or computer	System fails	Replace cord Watch out not to damage it in use			Cord damaged in use
		Trip over / get pulled	No image / user interface Pull computer of table	System fails	Place cord out of the way			User interacting with cable
Touch-screen power cord	Transport electricity	No conduction	No power to screen	System fails	Replace cord Watch out not to damage it in use			Cord damaged in use
		Not connected	No power to screen	System fails	Connect cord			Cord not plugged in
		Short circuit	Fuse of power filter will blow.	System fails	Replace cord Watch out not to damage it in use			Cord damaged in use
Touch-screen	Display data from computer	No connection	No image on screen	System fails	Check connections			
		Wrong resolution	No or incorrect image on screen	System fails	Reset settings			
		Falling of table	Pull cables or other equipment	System fails	Tighten holding clamp tightly			

	User input	Wrong calibration	No or wrong user input	Delay possible failure	Calibration on start-up			
		No input registration	No user input	System fails	Replace screen			
	Input to computer	No connection	No user input	System fails	Check connections			
USB cable	Transport signal from hub to computer	No connection	No data to computer	System fails	Alarm on screen Connect or replace cord Watch out not to damage it in use			Cord not plugged in Cord damaged in use
		Not connected	No data to computer	System fails	Alarm on screen Connect cord			Cord not plugged in
		Short circuit	No data to computer	System fails	Alarm on screen Replace cord Watch out not to damage it in use			Cord damaged in use
		Trip over / get pulled	No data to computer Pull computer of table	System fails	Place cord out of the way			User interacting with cable
USB-Serial Hub	Coverts Serial connection to USB	No signal	No input from sensors	System fails	Alarm on screen Check connections and replace if necessary			
		Falling of table	Pull cables or other equipment	System fails	Place stable on table			
Serial cable	Transport signal from pulseoximeter to hub	No conduction	No data to computer	System fails	Alarm on screen Replace cord Watch out not to damage it in use			Cord not plugged in Cord damaged in use
		Not connected	No data to computer	System fails	Alarm on screen Connect cord			Cord not plugged in

		Short circuit	No data to computer	System fails	Alarm on screen Replace cord Watch out not to damage it in use			Cord damaged in use
		Trip over / get pulled	No data to computer Pull equipment of table	System fails	Cord placed out of the way			User interacting with cable
Pulse-oximeter	Data from SpO$_2$ sensor	No input	No data	System fails	Alarm on screen Alarm on pulseoximeter			
	Intrepid measurement	Dys-hemoglobin's	Incorrect or no data to computer	System fails	Dealt with by pulseoximeter manufacturer			
		Motion artefact	Incorrect or no data to computer	System fails	Dealt with by pulseoximeter manufacturer			
		Reductions in peripheral pulsation	Incorrect or no data to computer	System fails	Dealt with by pulseoximeter manufacturer			
		Venous pulsations	Incorrect or no data to computer	System fails	Dealt with by pulseoximeter manufacturer			
		Acquisition time	Reduced accuracy or loss of high frequency data	System fails	Dealt with by pulseoximeter manufacturer			
		Falling of table	Pull cables or other equipment	System fails	Place stable on table			
	Data to computer	Unable to obtain a measurement or interpret the measurement	No data to computer	System fails	Alarm on screen			
SpO$_2$ sensor	Obtain measurement	Penumbra effect	Incorrect or no data to computer	System fails	Dealt with by pulseoximeter manufacturer			

		Ambient light	Incorrect or no data to computer	System fails	Cover sensor			
	Transport signal	No conduction	No data to pulseoximeter	System fails	Alarm on screen Replace cord Watch out not to damage it in use			Cord not plugged in Cord damaged in use
		Not connected	No data to pulseoximeter	System fails	Connect cord			
		Short circuit	No data to pulseoximeter	System fails	Alarm on screen Replace cord Watch out not to damage it in use			Cord damaged in use
Serial cable	Transport signal from oxygen monitor to hub	No conduction	No data to computer	System fails	Alarm on screen Replace cord Watch out not to damage it in use			Cord not plugged in Cord damaged in use
		Not connected	No data to computer	System fails	Alarm on screen Connect cord			Cord not plugged in
		Short circuit	No data to computer	System fails	Alarm on screen Replace cord Watch out not to damage it in use			Cord damaged in use
		Trip over / get pulled	No data to computer Pull equipment of table	System fails	Cord placed out of the way			User interacting with cable
Oxygen monitor	Data from oxygen sensor	No connection	No data	System fails	Alarm on screen Check connections			
		No battery power	No power	System fails	Alarm on screen Replace batteries			
	Interpret measurement	Wrong calibration	Incorrect data	System fails	Calibrate oxygen monitor			

		No battery power	No power	System fails	Alarm on screen Replace batteries			
		Falling of table	Pull cables or other equipment	System fails	Place stable on table			
	Data to computer	No connection	No data to computer	System fails	Alarm on screen Check connections			
		No battery power	No data to computer	System fails	Alarm on screen Replace batteries			
Sensor cable	Transport signal from oxygen sensor to oxygen monitor	No conduction	No data to monitor	System fails	Alarm on screen Replace cord Watch out not to damage it in use			Cord not plugged in Cord damaged in use
		Not connected	No data to monitor	System fails	Alarm on screen Connect cord			Cord not plugged in
		Short circuit	No data to monitor	System fails	Alarm on screen Replace cord Watch out not to damage it in use			Cord damaged in use
		Trip over / get pulled	No data to computer Pull equipment of table	System fails	Cord placed out of the way			User interacting with cable
Oxygen sensor	Measure oxygen fraction	Sensor expired	Incorrect or no data	System fails	Replacement of sensor if calibration fails			
		Blocked airflow	Incorrect or no data	System fails	Check measurement during calibration			
	Data to oxygen monitor	No connection	No data to monitor	System fails	Alarm on screen Check connections			
Software	See separate table							

Table 16: FMEA of the software of ASOR.

1. ID	2. function / oper. status	3. failure mode	4. effect on other parts	5. effect on system	6. measures	7. fail frequency	8. ranking effect	causes / remarks
Software	Overall	Software crash	No image to screen, or frozen	System fails				
	Timing	To slow	Update frequency low	Slow response	Separate steps with their own timers, with one overall display loop Fast enough computer			Read_Out_800_600_V1.vi
		Not synchronous	None	None	Separate steps with their own timers, with one overall display loop			Read_Out_800_600_V1.vi
	Readout Pulseoximeter	Wrong output: Status update instead of measurement	None	None	Check if measurement is within range and correctly formatted			SpO2FaultCheck.vi
		Incorrect measurement (see pulseoximeter)	Data displayed incorrectly	Incorrect data provided to physician	Check if measurement is within range and correctly formatted			SpO2FaultCheck.vi
		No measurement		System fails	Alarm Check hardware			Read_Out_800_600_V1.vi
	Readout Oxygen monitor	No measurement		System fails	Alarm Check hardware			Read_Out_800_600_V1.vi

Convert pulseoximeter data to SpO$_2$ and Pulse data	Conversion error	Data displayed incorrectly	Incorrect data provided to physician	Check if measurement is within range Directly displayed on screen			Read_Out_800_600_V1.vi
Convert oxygen monitor data to FiO$_2$	Conversion error	Data displayed incorrectly	Incorrect data provided to physician	Check if measurement is within range Directly displayed on screen			Read_Out_800_600_V1.vi
Store data	Not enough space on hard disk	Software stops running, gives error	System fails	Check available space			Read_Out_800_600_V1.vi
Display data	Data not displayed			Directly in readout loop			Read_Out_800_600_V1.vi
	Incorrect data displayed			Check if measurement is within range and correctly formatted			SpO2FaultCheck.vi
	To small		System fails	Designed in accordance to: NPR 7022 Functional use of colour - Accommodating colour vision disorders			User with bad eyes
Display data in graph	Confusion over plotted data		System fails	Designed in accordance to: NPR 7022, Functional use of colour - Accommodating colour vision disorders			PrebForGraph.vi

		Data out of bounds	None		Scale graph to include measurements			Scale_Graph.vi
	Target SpO₂				Targets loaded from separate file for all uses			TargetSpO2.vi
	Start program							StartScreen.vi
	Select resuscitation table	Incorrect selection	No measurement data	System fails	Visual feedback of selection, error if none is selected			UserInput.vi
	Start resuscitation							StartScreen.vi
	Stop resuscitation							StartScreen.vi
	Display data of entire resuscitation							Summary.vi
		Buffer to small (longer than an hour)	System hangs	System fails	Guarantied buffer for at least 1 hour			Read_Out_800_600_V1.vi
	Close program							StartScreen.vi
	Alarm (no hub)							ErrorMsg.vi ErrorMsgFiO2.vi ErrorMsgSpO2.vi
	Alarm (no Oxygen monitor)							ErrorMsg.vi ErrorMsgFiO2.vi
	Alarm (no Pulseoximeter)							ErrorMsg.vi ErrorMsgSpO2.vi

Alarm (SpO$_2$)							Readout_800_600_V1.vi
Alarm (Pulse)							Readout_800_600_V1.vi
Alarm (FiO$_2$)							Readout_800_600_V1.vi

Table 17: Additional FMEA for the software of the advice given by ASOR version 2.

1. ID	2. function / oper. status	3. failure mode	4. effect on other parts	5. effect on system	6. measures	7. fail frequency	8. ranking effect	causes / remarks
Software	Advice on when to adjust FiO_2	No measurements	No advice given					Yet to name as sub vi
		False measurements	Bad advice	System fails Endanger patient	Averaging of the measurements Averaging of the advice			Yet to name as sub vi
		Response time	Bad advice	System fails Endanger patient	Timeout after FiO_2 adjustment Time out after obtaining SpO2 signal			Yet to name as sub vi
	Advice on FiO_2 step size	No measurements	No advice given					Yet to name as sub vi
		False measurements	Bad advice	System fails Endanger patient	Averaging of the measurements Averaging of the advice Limit step size			Yet to name as sub vi
		Response time	Bad advice	System fails Endanger patient	Timeout after FiO_2 adjustment Time out after obtaining SpO_2 signal			Yet to name as sub vi

RESEARCH PROTOCOL

Advisory System for Supplemental Oxygen Therapy during Resuscitation of preterm infants.

Advisory System for Supplemental Oxygen Therapy during Resuscitation of preterm infants.

Protocol ID	ASOR
Short title	Advisory System for Oxygen during Resuscitation of preterm infants.
Version	1
Date	September 20th, 2011
Coordinating investigator/project leader	Drs. D. Rook Erasmus MC - Sophia Children's Hospital Department of Pediatrics Division of Neonatology Room Sp-3433 Dr. Molewaterplein 60 Postbus 2060 3000 CB Rotterdam tel: +31(0)10 7037008 d.rook.1@erasmusmc.nl
Principal investigator(s)	T.G. Goos Erasmus MC - Sophia Children's Hospital Department of Pediatrics Room Sp-2210 Dr. Molewaterplein 60 Postbus 2060 3000 CB Rotterdam Delft University of Technology Faculty of Mechanical, Maritime and Materials Engineering Department of Biomechanical Engineering Mekelweg 2 2628 CD Delft mob: +31(0)6 41859608 t.goos@erasmusmc.nl

Sponsor (in Dutch: verrichter/opdrachtgever)	Erasmus MC - Sophia's Children's Hospital Department of Pediatrics Division of Neonatology Postbus 2060 Dr. Molewaterplein 60 3000 CB Rotterdam Delft University of Technology Faculty of Mechanical, Maritime and Materials Engineering Department of Biomechanical Engineering Mekelweg 2 2628 CD Delft
Independent physician(s)	Dr. K. Joosten Pediatrician-intensivist Erasmus MC - Sophia Children's Hospital Department of Pediatrics Division of Pediatrics Intensive Care Room Sk-3280 Dr. Molewaterplein 60 Postbus 2060 3000 CB Rotterdam tel: +31(0)10 7037029 k.joosten@erasmusmc.nl

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Sponsor or legal representative: For non-commercial research, Head of Department: Dr. I.K.M. Reiss Head of Neonatology department Erasmus MC - Sophia Children's Hospital Department of Pediatrics Division of Neonatology Room Sp-3432 Dr. Molewaterplein 60 Postbus 2060 3000 CB Rotterdam tel: +31(0)10 7036077 i.reiss@erasmusmc.nl		
Coordinating Investigator/Project leader/Principal Investigator: Drs. D. Rook Erasmus MC - Sophia Children's Hospital Department of Pediatrics Division of Neonatology Room Sp-3433 Dr. Molewaterplein 60 Postbus 2060 3000 CB Rotterdam tel: +31(0)10 70 37008 d.rook.1@erasmusmc.nl T.G. Goos Delft University of Technology Faculty of Mechanical, Maritime and Materials Engineering Department of Biomechanical Engineering Mekelweg 2 2628 CD Delft mob: +31(0)6 41859608 t.goos@erasmusmc.nl		

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee
AE	Adverse Event
AR	Adverse Reaction
ASOR	Advisory System for Oxygen during Resuscitation
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
FiO2	Fraction of Inspired Oxygen
GCP	Good Clinical Practice
HR	Heart Rate
IB	Investigator's Brochure
IC	Informed Consent
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
METC	Medical research ethics committee (MREC)
NICU	Neonatal Intensive Care Unit
OR	Operating Room
(S)AE	(Serious) Adverse Event
SPC	Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)
SpO2	Oxygen Saturation as measured by pulse oximetry
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
Wbp	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: Ten percent of all newborn infants need active resuscitation after birth in order to stabilize them [2]. The majority of those infants in need of active resuscitation are born premature. Due to immature lungs, preterm infants often need respiratory support and supplemental oxygen therapy [3].

Unfortunately, supplemental oxygen therapy is associated with under or over exposure to oxygen. The resulting hypoxia or hyperoxia can result in a.o. damage to the eyes [4, 5], the brains [6, 7], the hearth and kidneys [8], and even death [9, 10].

The oxygen saturation (SpO_2), measured by pulse oximetry, is controlled by manually adjusting the fraction of inspired oxygen (FiO_2).The European Resuscitation Council (ERC) guidelines [1] specify SpO_2 targets at specific times after birth (shown in Figure 1, page 10). Manual control of the SpO_2 is difficult because it changes frequently [11, 12], the pulse oximeter has a low accuracy [12-15], and there is no unambiguous relation between FiO_2 and SpO_2 [13, 16].

Ideal would be to monitor and control the SpO2 continuous. But the resuscitation room is a challenging environment [17], and other tasks that must be performed, will often hinder the undivided attention and continuous control.

The Advisory System for Oxygen during Resuscitation (ASOR) is developed to improve the control of the SpO_2 during the first minutes of life. The improvement is achieved by reminding the physician when FiO_2 adjustments should be made, and advising him on the new FiO_2. The ASOR will consists of a monitor; displaying all relevant measurements and their trends (heart rate, time since birth, SpO_2 and FiO_2) together on a single screen. The ASOR will alert the physician when FiO2 adjustments are necessary, and display the suggested new FiO_2 based on the measured and trend of the SpO_2, HR, and FiO_2. In the future, the ASOR can be developed further, to be used as a fully automatic adjustment device for the FiO_2.

Objective: To determine the practical usability of the ASOR in clinical practice. By studying to what extend it is able to remind the physician when FiO_2 adjustments are necessary, and give advice that is followed, during de resuscitation of preterm infants.

Study design: During resuscitation of preterm infants, all relevant parameters (FiO_2, SpO_2, HR) will be recorded and analysed. The first part of the study is used to form a baseline, and together with data collected as part of the "Glutathione availability in neonates" study (MEC 2005-016) is used to further optimise the advise that the ASOR will give.

During the second part of the study, the physician is reminded by the ASOR when the FiO_2 needs to be adjusted, and will receive advise from the ASOR on the new FiO_2. This advise is based on the measured parameters and their trends, together with SpO_2 targets. The physician will receive instructions that he or she is free to either follow the advice, or ignore it. Observations and an interview with the physician immediately after the resuscitation will be used to find out if the ASOR is useful in clinical practice. The results of the resuscitation with the ASOR will be compared to the current practice to assess the improvement.

Study population: For the first part of the study, in which only data will be recorded of current clinical practice, we aim to include 20 preterm infants, born at a gestational age of < 32 weeks. For the second part, an additional twenty preterm infants will be included. The preterm infants included in this study should require additional oxygen (FiO_2 > 21%) during the resuscitation directly after birth.

Intervention (if applicable): There are no direct interventions. Thus, i.e. there will be no change in the resuscitation protocol or the sensors applied to the patient. The only changes are how information is displayed, and the reminder and suggestion given by the ASOR when adjusting of the FiO_2 is needed. The physician can decide either to follow or to ignore this advice.

Main study parameters/endpoints: The main study parameter is how often the physician concurs with the advice given by the ASOR, both on when to adjust the FiO_2, and with what step size.

To quantify the performance, the deviation of the SpO_2 from the SpO_2 targets as stated in the guidelines [1] will be compared for routine care with and without the ASOR.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Due to the observational character of this study, the risks are very small. The study needs to be performed on this specific group of ventilated very preterm infants during resuscitation, because the physiological behaviour of these instable patients is unique and cannot be simulated.

1.   INTRODUCTION AND RATIONALE

Ten percent of all newborn infants need active resuscitation after birth in order to stabilize them [2]. In the Netherlands, this were approximately 1800 infants in 2010 [18], a number that is rising each year [19]. The majority of the infants that need active resuscitation are born premature. Due to immature lungs, preterm infants often need respiratory support and supplemental oxygen therapy.[3].

Unfortunately, supplemental oxygen therapy is associated with under or over exposure to oxygen. The resulting hypoxia or hyperoxia can result in a.o. damage to the eyes [4, 5], the brain [6, 7], the hearth and kidneys [8], and even death [9, 10].

Currently, the fraction of inspired oxygen (FiO_2) supplied to the preterm infant is adjusted manually by the caregiver. The decision to adjust FiO_2 is mainly based on the measurement of the oxygen saturation by pulse oximetry (SpO_2) and the pulse rate. Literature shows that the manual control of the SpO_2 level in preterm infants is difficult and time consuming for several reasons:

- The SpO_2 levels change frequently and are unpredictable due to the underdevelopment of the lungs and brain [11, 12];
- Pulse oximetry is influenced by artefacts which cause a low accuracy [12, 15];
- There is no unambiguous relation determined between FiO_2 and SpO_2 [13, 16];

Due to these difficulties, only 50% of the time is spent within the intended SpO_2 range during routine care in the Neonatal Intensive Care Unit (NICU) [20-22]. Also predicting the trend of the SpO_2 level is a difficult task, which is especially important during the first 10 minutes after birth, when the SpO_2 is meant to rise. Misjudging the trend will result in overshooting the target, which exposes the infant to unwanted SpO_2 levels, and additional fluctuations.

An (semi-) automatic controller could keep SpO_2 at a more constant level by adjusting the FiO_2 automatically, and continuous, and reduce high SpO_2 levels due to overshoot. Worldwide several groups have developed (semi-) automatic controllers for SpO_2 in a NICU setting, with promising results [23-28]. These controllers adjust FiO_2 (semi) automatically, when SpO_2 deviates from the target. Research resulted in the first commercially available ventilator that is able to automatically adjust the FiO_2 based on SpO_2 measurement, the Avea ventilator (with addition of the $CliO_2$ module) by CareFusion [29]. Unfortunately, this device is not suitable for the use during resuscitation. One of the reasons that the device cannot be used during resuscitation is the fact that the target SpO_2 during resuscitation depends on the time after birth.

The target SpO_2 values are based on the guidelines of the European Resuscitation Council (ERC) in 2011 (Figure 1, page 10).These guidelines indicate acceptable SpO_2 levels during the first 10 minutes after birth, after which the upper and lower saturation limits are used as in the NICU.
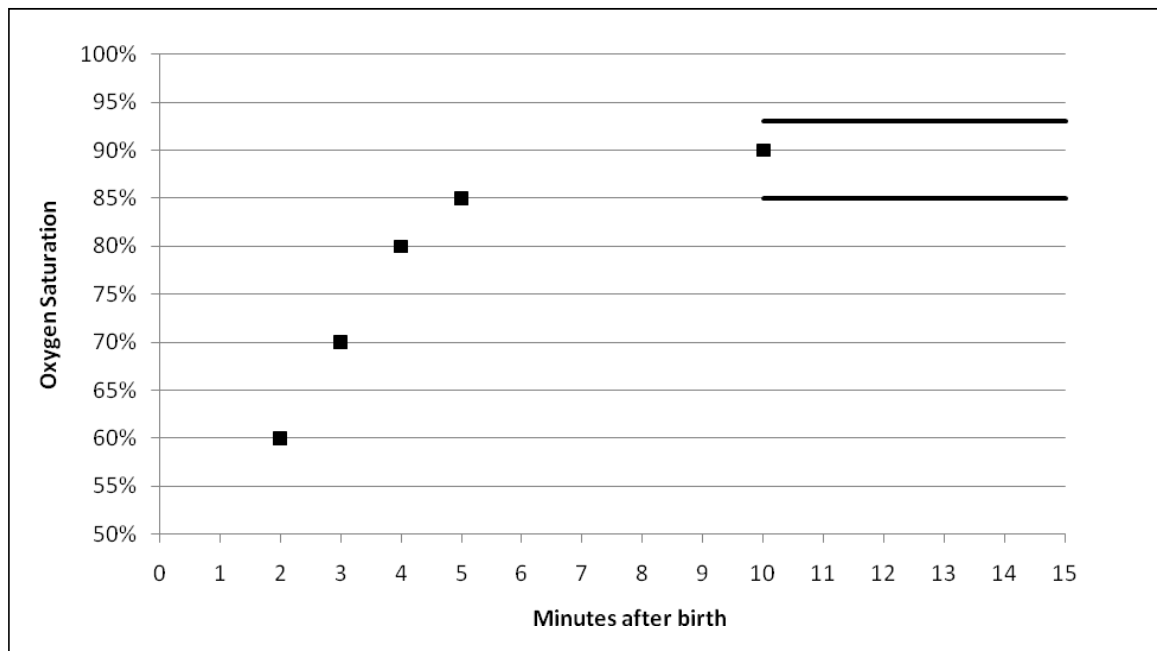
Figure 1: Saturation targets at specific times after birth as specified by the ERC [1], and the high and low saturation limits used after 10 minutes after birth, as used in the NICU of the Erasmus MC.

Although the ERC guidelines give target SpO_2 levels at specific times after birth, no advice is given on how these targets should be achieved. The previous guidelines from 2005 suggested starting with a FiO_2 of 100% whenever additional oxygen was needed. The current 2010 version suggest starting with room air and adjusting it according to the measured SpO_2. However, in has been shown that almost all very preterm infants need additional oxygen during resuscitation [4, 30]. Currently, a study on the optimal FiO_2 to start resuscitation of preterm infants is being performed at the Erasmus MC-Sophia Children's Hospital (MEC 2005-016). But how to subsequently adjust the FiO_2 during resuscitation is still unknown and left to the caregiver to decide.

The difficulty is that during the first few minutes hypoxia needs to be avoided, which is done by giving additional oxygen. The resulting faster rise and higher FiO_2 will often result in overshooting the intended SpO_2 target and in hyperoxia. Ideal would be to monitor and control the SpO_2 continuous. But the hectic nature of resuscitation, and other tasks that must be performed, will often hinder the undivided attention and continuous control.

In a cooperation between the Erasmus MC and the Delft University of Technology, the Advisory System for Oxygen during Resuscitation (ASOR) is developed. The ASOR, an aid for the physician to improve control of SpO_2, provides:

1) An overview of all relevant parameters for resuscitation (a.o. SpO_2, HR, FiO_2, time after birth) on a single screen.
2) A graphical overview of the trends of all relevant parameters (e.g.SpO_2, HR, and FiO_2), as well as the SpO_2 targets from the ERC guidelines [1].
3) A reminder to the physician when the FiO_2 needs to be adjusted when SpO_2 deviates from the target, and display a new suggested FiO_2.

The simultaneous displayed trends and targets, reminder on when to adjust, and the suggestion for the FiO_2, will probably make the control of the SpO_2 and the adjustment of the FiO_2 easier.

The advise is based on a combination of the trends and the values of SpO_2, HR, and FiO_2 and the error between the current SpO_2 value and the SpO_2 target value, in accordance to the ERC guidelines [1]. Data from the "Glutathione availability in neonates" study (MEC 2005-016), is used to validate the advice given by the ASOR. This study includes data on more than 175 preterm infants, with continuous measurement of their SpO_2, HR and FiO_2 during the entire resuscitation.

2. OBJECTIVES

Primary Objective:

To determine the practical usability of the ASOR in clinical practice. By studying to what extend it is able to remind the physician when FiO_2 adjustments are necessary, and give advice that is followed, during de resuscitation of preterm infants.

Secondary Objective(s):

To compare the resuscitation using ASOR to current clinical practice. This comparison will be made over the total resuscitation period, and separate for the first 10 minute after birth during which the SpO_2 should rise, and the "stable" period afterwards (Figure 1, page 10). The performance will be assessed based on the following parameters;

- deviations of the SpO_2 from the SpO_2 targets;
- duration of the periods that SpO_2 is outside of saturation targets;
- frequency and step sizes of the adjustments in the FiO_2;

3. STUDY DESIGN

In the first part of this study, data is recorded from resuscitation of preterm infants according to current clinical practice. Although data is available from the "Glutathione availability in neonates" study (MEC 2005-016), additional data is needed from infants that did not receive interventions (prenatal steroids) before birth.

The data is collected by reading out the pulse oximeter as normally used during resuscitation, and by an oxygen sensor placed in the oxygen blender to read out the FiO_2 that is administered. This sensor is already present as part of the 'Glutathione availability in neonates' study. No additional sensors are placed on the patient, nor is routine care changed. An overview of the recorded parameters can be found in Table 1 (page FFF).

From the first twenty patients the data is recorded every second. This recorded data is used for two purposes:
1) To further optimize the suggestion model of the ASOR afterwards.
2) To function as a baseline, in order to compare with the results of the resuscitation with the ASOR in use.

In the second part of this study, the second group of twenty patients is resuscitated while the ASOR is present in the resuscitation room, and will remind the physician when the FiO_2 needs to be adjusted, and advise him on a new FiO_2.

Before the resuscitation, the physician receives instructions that he is free to follow the advice of the ASOR, or ignore it.

During the resuscitations where the ASOR is used, the principal investigator will be present to take care of the ASOR and observe. If during the resuscitation the advice given by the ASOR is not useful for the physician, a notation will be made. After the resuscitation, the principal investigator and the physician will assess the data to find out why the advice was not useful. Just as in the first part of this study, the data is recorded. The data from both patients groups will be compared. The data recording starts at the moment the preterm infant is brought into the resuscitation area, and will be continued until the infant is transferred from the resuscitation room to elsewhere.

3.1 Experimental setup
The parameters that are recorded during the total resuscitation period are listed in Table 1 (page FFF). A complete list of all materials used can be found in Table 2 (page FFF). The sensors and instruments used to obtain these measurements are the same as the ones used in the current 'Glutathione availability in neonates' study (MEC 2005-016), with the addition of a computer and monitor to display the data and calculate the advice. There are no additional sensors placed on the infant compared to routine care.

Table 1: Recorded parameters

Parameter	Abbreviation	Obtained by
Oxygen saturation	SpO_2	Pulse oximeter
Heart rate	HR	Pulse oximeter
Fraction of inspired oxygen	FiO_2	Oxygen analyser

Table 2: Products used for data acquisition and display

Product	Brand and Version
Pulse oximeter	Nellcor OxiMax N-600x
Oxygen analyser	Teledyne MX300 Medical Oxygen Monitor
Oxygen sensor	Teledyne R-17MED
Serial to USB converter	Moxa UPort 1410
Software	National Instruments Labview 2009 Service Pack 1 Version 9.0.1
Computer	Medical computer or laptop with balanced power supply running Windows
Monitor	Generic LCD monitor

4.   STUDY POPULATION

4.1   Population (base)

All preterm infants resuscitated directly after birth in the delivery room, or Operating Room (OR), of the Erasmus Medical Center, Sophia Children's Hospital that need additional oxygen are eligible for this study. We will observe and record data on a total of 40 preterm infants.

These infants are divided in two equal groups. From the first group the data obtained during the resuscitation is recorded. During the resuscitation of the second group of twenty infants, the ASOR will be present to provide a reminder and advice to the physician whenever FiO_2 adjustments are needed.

4.2   Inclusion criteria

To be eligible for this study the preterm infant should have been born at a gestational age of less than 32 weeks, and have the need for supplemental oxygen ($FiO_2 > 21\%$) during the resuscitation immediately after birth.

4.3   Exclusion criteria

Infants with any known congenital or chromosomal defects will be excluded from this study.

4.4   Sample size calculation

This study is a pilot study with a limited number of participants. The goal of the study is to study to which extent the ASOR is useful during de resuscitation of preterm infants.

A routine resuscitation of a preterm infant lasts about 30 minutes. Within this time period, approximately 10 FiO_2 adjustments are performed. Thus, despite the relative small number of patients included in the study, there will be enough recorded FiO_2 adjustments (±200 adjustments) to determine whether the ASOR will be helpful during resuscitation or not.

5. METHODS

5.1 Study parameters/endpoints

5.1.1 Main study parameter/endpoint

The focus is on the number of times the ASOK reminds the physician to adjust the FiO_2, and if he or she concurs with the suggested FiO_2.

Whether or not the physician concurs can be seen from the recorded data. If he concurs the data will show a change of the FiO_2, and if the suggested FiO_2 is correct, will change to that fraction. Observation by the principal investigator during the resuscitation will tell if the physician takes note of the reminders and suggestions. An interview immediately after the resuscitation will be taken in order to assess the usability of the ASOR during clinical practice.

5.1.2 Secondary study parameters/endpoints (if applicable)

The parameters shown in **Table** (page 14) will be recorded and analyzed afterwards in order to compare routine resuscitations, with resuscitations were the ASOR is used.

5.2 Study procedures

The infants are resuscitated as normal, in compliance with the current guidelines [1]. There are no additional sensors used on the patient. The ASOR only adds a monitor that shows the measured parameters (Table, page 14) with their trends on a single screen, it will alert the physician when a FiO2 adjustment is needed, and it will display advise on the FiO_2 that should be administered.

The ASOR requires no input or adjustments during the resuscitation procedure. The principal investigator will be present to set up the ASOR. The physician will receive instructions that he should be critical about the advice he is given, and is free to either follow or ignore it.

6. SAFETY REPORTING

6.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

6.2 Adverse and serious adverse events

No interventions are performed in order to do this study, so there is no possibility of adverse events.

7.   STATISTICAL ANALYSIS

7.1   Descriptive statistics

Demographic characteristics of the study population will be described. The gestational age, the birth weight, and the kind of respiratory support will be described as well as acute incidents like i.e. sepsis. Also, any other information that could have an influence on the oxygen therapy will be analyzed and described.

7.2   Univariate analysis

The percentage of times the reminder actually resulted in a FiO_2 adjustment (with the suggested step size) will be calculated.
The standard deviation (SD) of the error between the SpO_2 and the target SpO_2 will be determined.

7.3   Multivariate analysis

To improve the suggestions made by the ASOR, the reminders and the suggestions that resulted in FiO_2 adjustment will be studied in relation with the gestational age and birth weight.
Several parameters will be explored by multivariate analysis. We will study correlations between the parameters recorded for this study (see Table 1, page FFF).

7.4   Interim analysis

This study is a pilot study, thus we don't have the required information to determine a sample size by using statistical analysis. Based on experience of the coordinating investigator we decided that a sample size of 20 subjects per group will provide the information we need.
The number of subjects enrolled for this study might seem small, however during routine resuscitation approximately 10 adjustments in the FiO_2 are preformed [31].

8. ETHICAL CONSIDERATIONS

8.1 Regulation statement

The study will be conducted in accordance to the principles of the Declaration of Helsinki version 2004 (www.wma.net), and the investigators comply with the principles enunciated in this declaration.

8.2 Recruitment and consent

We suggest that informed consent is not necessary because there are no interventions. Resuscitation of the preterm infants is done are described in the ERC guidelines [1].

8.3 Benefits and risks assessment, group relatedness

For the infants enrolled in this study there is no added benefit or risk.

8.4 Compensation for injury

The sponsor has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

9. ADMINISTRATIVE ASPECTS AND PUBLICATION

9.1 Handling and storage of data and documents

The recorded data will be accessible for the investigators and a technician of the Sophia's Children's Hospital (A.G. Koedood). In the recorded data, patients can be identified by an identification number. Forms and data will be kept for 15 years.

9.2 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the completion of the 10th resuscitation.

In case the study is ended prematurely, the investigator will notify the accredited METC, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC. In case the final study report will not be available within one year, another term will be defined including the reasons.

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A.9 DATA ACQUISITION SOFTWARE FOR THE "OXYGEN STUDY"

Software was developed for the ongoing research into the optimal starting FiO$_2$ during the resuscitation of preterm infants, "Glutathion beschikbaarheid in pasgeborenen, deel onderzoek Zuurstof-B" conducted at the Erasmus Medical Centre (Rotterdam, The Netherlands).
The developed software reads out all the measurements from two resuscitation stations, and saves it to an Excel file. The software is similar to the ASOR in its basic setup, the same loop structure is used to ensure synchronised storage of the measurements. It replaced 4 separate programmes that had to be synchronised afterwards based on video recordings.
It is continuously in use, for the duration of the study, to capture the data from all 6 resuscitation area's at the Erasmus Medical Centre.

A.10   ATTENDED CONGRESSES / SYMPOSIA / PROMOTIONS

26-10-2011   2nd Brussels Neonatology Symposium, Hôpital Erasme, Brussels, Belgium

21-12-2011   Promotion Drs. André A. Kroon, Erasmus MC, Rotterdam, the Netherlands.
"Ventilation-introduced Alterations in Lung Development".

21-12-2011   De wereld van BPD (The world of Bronchopulmonary Dysplasia), Erasmus Medical Centre, Rotterdam, the Netherlands

16-02-2012   New Insights into Neonatal Resuscitation, Leiden University Medical Center, Leiden, the Netherlands

12-04-2012   Third Dutch Neonatal Fellow Meeting, Utrecht Medical Center, Utrecht, the
and   Netherlands
13-04-2012   Presented results: "Resuscitation of preterm infants: Are we able to follow the oxygen saturation targets?"

15-04-2012   Submitted abstract for 4th Congress of the European Academy of Paediatric Societies (EAPS): "Improving control of the oxygen saturation during resuscitation of preterm infants with the use of trend monitoring"

03-05-2012   Submitted article; "Observing the resuscitation of very preterm infants; Are we able to follow the oxygen saturation targets" to Archives of Disease in Childhood, the Fetal and Neonatal edition.

01-06-2012   Symposium Study Design: Beyond Simple Randomization

24-09-2012   Promotion Ir. A.C. van der Eijk, Delft technical university, Delft, the Netherlands "On-ward observations in neonatal intensive care: Towards safer supplemental oxygen & IV therapy"

26-09-2012   Promotion Drs. Lisha Huang, Erasmus MC, Rotterdam, the Netherlands.
"The essential amino acid requirements of infants".

26-09-2012   Promotion Drs. Femke Maingay de Groof, Erasmus MC, Rotterdam, the Netherlands.
"The Branched-Chain Amino Acid Requirement in Neonates".

05-10-2012   4th Congress of the European Academy of Paediatric Societies (EAPS),
till   Istanbul, Turkey.
09-10-2012   Presented: "Improving control of the oxygen saturation during resuscitation of preterm infants with the use of trend monitoring" as a poster.
21 CME credits

29-10-2012   Submitted article; "Observing the resuscitation of very preterm infants: Are we able to follow the oxygen saturation targets?" to Resuscitation.

07-11-2012   Symposium "Cerebral and Somatic Oxygenation, the art of non-invasice measurements in neonatology", Beatrix Children's Hospital, Groningen, the Netherlands.

12-11-2012 till 16-11-2012	Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (BROK) (Good clinical practice)
20-11-2012	Exam "Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (BROK)" Passed with 88%, 1 ECTS
10-12-2012 till 13-12-2012	Visited Department of Paediatrics, Division of Neonatology, Medical University Graz, Graz, Austria Presented study methodology and results of the conducted observational study and the ASOR
21-12-2012	Gave a presentation on pregnancy and fetal development for the course Physiological systems at the TU Delft
08-01-2013 till 18-01-2013	Hour long educational sessions for the nursing staff on Near Infra-Red Spectroscopy and the INOVS device
12-01-2013	Submitted revised version of article; "Observing the resuscitation of very preterm infants: Are we able to follow the oxygen saturation targets?" to Resuscitation.
21-01-2013	"Observing the resuscitation of very preterm infants: Are we able to follow the oxygen saturation targets?" accepted for publication in Resuscitation.
07-02-2013	Mini course "Methodology of patient research and preparing grant applications (Methodologie van Patiëntgebonden Onderzoek en Voorbereiding van Subsidieaanvragen)".
20-03-2013	Promotion Drs. Rob Taal, Erasmus MC, Rotterdam, the Netherlands. "Early Growth, Cardiovascular and renal development".
07-04-2013 till 08-04-2013	NVK - TULIPS Grant Writing & Presenting Weekend 2013
17-04-2013	Promotion Drs. Hester Vlaardingerbroek, Erasmus MC, Rotterdam, the Netherlands. "Content Matters!, Quantity and quality of parenteral nutrition for preterm infants".
17-04-2013	Promotion Drs. Denise Rook, Erasmus MC, Rotterdam, the Netherlands. "Less Stress, Oxidative stress and glutathione kinetics in preterm infants".
17-04-2013	Promotion Drs. Onno Helder, Erasmus MC, Rotterdam, the Netherlands. "Prevention of nosocomial bloodstream infections in preterm infants".
18-04-2013 till 19-04-2013	4th Dutch Neonatal Fellow Meeting Presented: "Controlling the oxygen saturation during the resuscitation of very preterm infants after caesarean section".