Automation of oxygen titration in preterm infants: current evidence and future challenges

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ABSTRACT

For the preterm infant with respiratory insufficiency requiring supplemental oxygen, tight control of oxygen saturation (SpO_2) is advocated, but difficult to achieve in practice. Automated control of oxygen delivery has emerged as a potential solution, with six control algorithms currently embedded in commercially-available respiratory support devices. To date, most clinical evaluations of these algorithms have been short-lived crossover studies, in which a benefit of automated over manual control of oxygen titration has been uniformly noted, along with a reduction in severe SpO_2 deviations and in need for manual FiO_2 adjustments. A single non-randomised study has examined the effect of implementation of automated oxygen control with the $CliO_2$ algorithm as standard care for preterm infants; no clear benefits in relation to clinical outcomes were noted, although duration of mechanical ventilation was lessened. The results of randomised controlled trials are awaited. Beyond the gathering of evidence regarding a treatment effect, we contend that there is a need for a better understanding of the function of contemporary control algorithms under a range of clinical conditions, further exploration of techniques of adaptation to individualise algorithm performance, and a concerted effort to apply this technology in low resource settings in which the majority of preterm infants receive care. Attainment of these goals will be paramount in optimisation of oxygen therapy for preterm infants globally.

INTRODUCTION

For the preterm infant with respiratory insufficiency requiring supplemental oxygen, evidence favours the targeting of a predetermined range of oxygen saturation (SpO_2), but achieving this with adequate precision is beyond the capacity of bedside clinicians, despite their best efforts. Manual adjustment of inspired oxygen concentration (FiO_2) is associated with a considerable proportion of time spent outside the target range for SpO_2. Automating the control of oxygen delivery in preterm infants has been seen as a logical goal for over four decades, and offers the hope of more effective SpO_2 targeting, and the benefits that may follow.

This review will examine the rationale for automated oxygen control in the preterm infant, survey the results of studies investigating its effect, and then explore some key challenges that remain for this technology. We contend that there is a need for: i) rigorously conducted randomised controlled trials of automated oxygen control, ii) a better understanding of the function and comparative performance of contemporary control algorithms, iii) enhancement and individualisation of algorithm performance through adaptation, and iv) application of this technology in low resource settings in which the majority of preterm infants receive care.

CURRENT EVIDENCE

The rationale for automated oxygen control in preterm infants

Oxygen therapy is a cornerstone of management for preterm infants with respiratory insufficiency, and over the years has aimed to overcome the long-recognized consequences of extreme hypoxaemia, including death and neurodevelopmental impairment [1-3]. More recent data from the SpO_2 targeting trials assembled by the NeOProM collaborators indicate that even mild hypoxia (SpO_2 target range 85-89%) imparts an additional mortality risk, at

least in the extremely preterm group [4]. However, on the other side of the therapeutic equation, infants born prematurely are uniquely vulnerable to iatrogenic hyperoxaemia, demonstrated in the early experience of oxygen-induced retinopathy of prematurity (ROP) [3], and reprised in the observation of increased ROP risk in infants in the higher SpO_2 range in the NeOProM analysis [4]. Taken together, these old and new findings cement the notion that oxygen therapy is a vital component of management for preterm infants with respiratory compromise, but that its delivery must be titrated to need.

Oxygen is currently administered to preterm infants using a legion of different respiratory support modes and interfaces. For the most part, these devices automatically blend air and oxygen to a desired FiO_2, although, as mentioned later in this review, in low resource settings FiO_2 is titrated through manual adjustment of the flow of oxygen and air. An approach of SpO_2 targeting is advocated [5,6] and widely used, whereby FiO_2 is titrated in an effort to maintain SpO_2 in a desired target range, commonly 90-95% or thereabouts. Unless automated titration of FiO_2 is available, this task falls to the bedside staff, and is known to be imperfectly accomplished, with a considerable proportion of time, and long continuous epochs, spent outside the target range limits [7-9]. Such observations provide, at least for the preterm infant, a clear rationale for automated oxygen control, a technology envisioned in the 1940s [10], explored in the 1970s [11], and enhanced and expanded in the decades thereafter.

Application of automated oxygen control algorithms in the preterm infant

Numerous algorithms for servo-controlled regulation of oxygen titration now exist and at least six [12-17] have been incorporated into devices commercially available for provision of respiratory support in preterm infants (Table 1). These algorithms function by comparison of an incoming SpO_2 reading with a desired set-point (either the mid-point or limits of the target

range) and calculation of an updated value for FiO_2, which is then actuated mechanically. The various approaches to oxygen control within these algorithms, and their performance in preterm infants, have been the subject of recent reviews [18-22]. The clinical investigations performed have in large part been crossover studies comparing the efficacy of automated with manual titration of oxygen, in groups of preterm infants mechanically ventilated [23-25], receiving non-invasive respiratory support [17,26-28], or receiving a mixture of these modalities [16,29-33], with considerable variation in the SpO_2 range being targeted (Fig. 1). When compared with manual oxygen control, automation of oxygen titration has uniformly been shown to be advantageous in crossover studies, with greater time in the SpO_2 target range (Fig. 1). Where reported, all infants have been noted to gain a benefit in some studies [17,26,27], but not others [28]. Other findings in common in these studies during application of automated oxygen control have been a lessening of time in, and episodes of, extreme deviations in oxygenation, and a reduction in the frequency of manual FiO_2 adjustments.

Some studies directly comparing function of different algorithms are starting to emerge [33,34]. The first of these head-to-head comparisons found no clear difference in the performance of a simple rule-based algorithm (CLAC) operating with either a 180 second or a 30 second lockout period after each FiO_2 adjustment [33]. The second head-to-head study found greater time in the SpO_2 target range with a modified proportional-integral-derivative (PID) algorithm (OxyGenie) compared with a hybrid rule-based and proportional-derivative (PD) algorithm ($CLiO_2$) [34]. Further crossover studies of this nature would help to refine our understanding of the comparative effectiveness of the different algorithms for automated oxygen control available for use in preterm infants. It is acknowledged that direct algorithm comparison studies are difficult to undertake, requiring access to the different devices in which the algorithms are embedded and a willingness amongst clinicians and parents to

support the crossover design that involves a changeover of respiratory support devices. As will be described below, bench testing of the different devices, including with an *in silico* simulation of oxygenation, offers the possibility of examining and comparing the function of oxygen control algorithms away from the clinical arena.

Longer-lasting benefits of automated oxygen control

The crossover design and short-lived nature of the studies included in Fig. 1 precludes any conclusion regarding a longer term effect of automated oxygen control in preterm infants. An examination for such effects will require studies of cohorts of infant assigned (ideally at random) to automated control of oxygen therapy or some form of control group, applied throughout the period of need for oxygen therapy. As yet, data from only two studies of this type are available, both non-randomised with a historical control group receiving manual oxygen titration. The first study in infants <30 weeks gestation reports the effects on oxygenation in a group receiving automated oxygen control using the $CLiO_2$ algorithm (n=21, median duration of oxygen therapy 11 days) compared with a pre-implementation group receiving manual control (n=21, median duration of oxygen therapy 3.3 days) [32]. Time in SpO_2 target range (90-95%) and time at different degrees of hypoxaemia and hyperoxaemia were determined, using SpO_2 and FiO_2 values sampled each minute from the bedside monitor. Infants receiving automated oxygen control had a higher proportion of time in target range (automated control group 62%; manual control group 48%; $P<0.01$), explicable by virtue of a decrease in time with SpO_2 >95% when receiving supplemental oxygen (19% vs 42%, $P<0.001$).

A further study from the same research group was the first to report on clinical outcomes for preterm infants managed either prior to or after adoption of automated oxygen control as

standard care [35]. The study compared clinical outcomes in 293 infants receiving manual oxygen titration with those of a group of 295 infants cared for after implementation of automated oxygen control with the CLiO$_2$ algorithm. No clear differences between the cohorts were noted in relation to mortality (10% vs 11%, p=0.81), necrotising enterocolitis (8.5% vs 9.2%, p=0.79), laser treatment for retinopathy of prematurity (5.2% vs 5.6%, p=0.84) and different degrees of bronchopulmonary dysplasia. There was, however, a shift to more non-invasive respiratory support in the post-implementation cohort, the relationship with automated oxygen control being unclear.

FUTURE CHALLENGES

Randomised controlled trials

As with medical therapies in general, ultimately only with randomised parallel group controlled studies will the impact of automated oxygen control be fully understood. As of now, one clinical trial is underway, the FiO$_2$-C study (NCT03168516) [36]. This pragmatic trial plans to recruit 2340 extremely preterm infants (<28 weeks gestation), with randomisation to automated oxygen control with any CE-marked algorithm/device, applied for as much time as possible whilst oxygen is being administered, or to routine manual oxygen control. There is no planned crossover. The primary outcome for the trial is the composite of death or any of severe ROP, bronchopulmonary dysplasia or necrotising enterocolitis. A co-primary outcome has been specified, that of the composite of death or any of i) language/cognitive delay, ii) motor impairment, iii) severe visual impairment or iv) hearing impairment, in each case assessed at 2 years corrected gestational age. The intervention cannot be blinded to treating clinicians but will be blinded to outcome assessors. The trial commenced in July 2018 and has currently recruited 570 infants (Dr. Axel Franz, personal communication, August 2021).

Understanding the function of the control algorithms

Devices incorporating an option for automated oxygen titration are becoming widely available, behoving clinicians (neonatal medical and nursing staff, respiratory therapists) to gain an understanding of what to expect from the oxygen control algorithm embedded within the respiratory support device they have at hand. This does not necessarily entail familiarity with the intricacies of algorithm logic, but rather an understanding of the likely algorithm response under a set of common circumstances, analogous to studies examining the waveforms generated by different high frequency oscillators [37].

We propose to conduct a multi-institutional collaborative study of the behaviour of each commercially-available oxygen control algorithm, using a protocol for bench-testing currently under development by one of the authors (HHS). The function of each device will be examined under controlled conditions simulating real patient care, with a respiratory support circuit in place. The SpO_2 input to the algorithm in each case will be a provided by a programmable SpO_2 simulator, and the FiO_2 output will be recorded via an oxygen analyser in the ventilator circuit. Important questions to be addressed will include how does the algorithm respond to unremitting minor and major hypoxaemia and hyperoxaemia, under what circumstances oscillation of SpO_2 can be induced, and what happens when the SpO_2 signal is missing for several minutes. The performance of the algorithm in SpO_2 targeting will also be examined using an *in silico* simulation of oxygenation [15]. Using abstracted oxygenation data reflecting a variety of clinical scenarios in preterm infants, a series of SpO_2 values will be input to the device under test, with the FiO_2 response generated by the algorithm logged, and used by the simulation to determine the next SpO_2 value in the

sequence. This work will allow clinicians to understand how a particular oxygen control algorithm responds in a range of clinical conditions.

Individualising algorithm performance through adaptation

Oxygen control algorithms can generally be categorised as being i) rule-based, ii) PD/PID or iii) adaptive [18,20], with several contemporary algorithms being hybrid algorithms with some adaptive components. In general terms an adaptive control algorithm is one that alters its behaviour to suit the prevailing conditions in the system under control, in this case the pathophysiology of oxygenation. Given the time variant and largely unpredictable nature of the neonatal oxygen transport system [38,39], the capacity for an oxygen control algorithm to adapt to changing circumstances appears to be a fundamental prerequisite for optimal SpO_2 targeting in the preterm infant. While a non-adaptive controller (e.g. a fixed rule-based algorithm) may be devised that performs well within a narrow band of the full spectrum of oxygenation disturbances, its performance will reduce as the system behaviour deviates further from this point. At least in simulation, an ill-suited oxygen controller can easily result in an unstable system in which SpO_2 oscillates (Fig. 2) [15]; in preterm infants such a controller has the potential to result in SpO_2 targeting that is considerably worse than manual oxygen titration.

As indicated above, several contemporary hybrid algorithms have an adaptive element in relation to the multiplier applied to the SpO_2 error to determine the output for the proportional term of the PD [12] or PID [15] algorithm. In both cases the resultant power of the algorithm is scaled up or down in direct proportion to the basal oxygen requirement, which in turn reflects the current severity the oxygen disturbance. It is known that the system gain (magnitude of the SpO_2 response to an FiO_2 adjustment) is inversely proportional to the

severity of lung disease [38]; hence more forceful FiO_2 alterations are needed to correct SpO_2 deviations in the diseased lung.

Fully adaptive oxygen control algorithms [39,40] operate by periodically estimating the current state of the oxygenation system (the "model"), which is then used to compute the FiO_2 adjustment required to achieve the desired change in SpO_2. In theory these algorithms can adjust themselves to achieve optimal control across the full spectrum of oxygenation disturbances (the "model space"). In practice, there are significant limitations imposed on the adaptability/generalisability of the algorithm by the shortcomings of the models used. Whilst highly accurate mathematical models of the neonatal oxygen transport system exist [41], they are not easily applied to controller design. Models that accurately reflect the real world are highly complex, making them computationally inefficient to estimate and often reliant on external inputs that may not be available in real-time at the bedspace of the preterm infant. To be suitable for use in an adaptive controller, a simplified model must be employed that can be updated rapidly enough to track the infants' change in state. Effective adaptive algorithms are also dependent on performance monitoring and self-tuning to ensure controller robustness across the model space.

An ideal oxygen control algorithm for the preterm infant would be sufficiently robust to achieve a base level of performance and stability across the model space, and be able to adapt for optimal performance as the model and operating point vary. The following will be needed in the development of such an algorithm:

1. Improved modelling to reflect the full dynamics of the neonatal oxygen transport system whilst remaining computationally feasible. Inclusion of additional inputs to the model, such as gestation, heart rate and respiratory rate, may also improve algorithm performance.

2. An algorithm design that allows tracking of the slow variation in basal oxygen requirement while remaining robust and responsive to sudden disturbances such as apnoea, bradycardia, and shunting.

3. Further incorporation of additional adaptive control techniques in the existing PID control algorithms to enhance their performance across the model space. The adoption of real-time model estimation techniques to adapt controller parameters during runtime would be a significant improvement on the predetermined rules that typically govern alterations in algorithm coefficients in response to changing disease severity. Auto-tuning techniques could also be incorporated to adjust controller parameters based on comparison between desired and historical performance in SpO_2 targeting. These potential effectiveness of these forms of adaptation is currently being examined by one of the authors (APM) using an *in silico* simulation.

4. An increased focus on oxygenation stability during automated oxygen titration, given the very real possibility that an ill-suited algorithm could worsen rather than improve control of oxygenation.

Application of automated oxygen control in low resource settings

The neonatal death rate in low- and middle-income countries, particularly in sub-Saharan Africa and South Asia, is more than nine times that of high income countries, with perinatal asphyxia and premature birth being the major contributors [42,43]. For the preterm infant born in a low-resource setting, respiratory distress syndrome and its complications remain a major threat to life, with high patient-to-nurse ratios as well as shortages of compressed air and oxygen sources, gas blenders, and pulse oximetry equipment contributing to the risk [44]. We consider that application of automated oxygen control systems, in a fully functional form but adapted to local conditions, should be seen as integral to the overall goal of providing

blended oxygen to preterm infants with respiratory insufficiency, regardless of their location in the world.

Currently, provision of respiratory support and supplemental oxygen for preterm infants in low- and middle-income countries is hampered by lack of availability of i) non-invasive respiratory support devices, ii) the facility for air-oxygen blending, iii) equipment to allow continuous oximetry [44], as well as iv) the shortage of trained healthcare workers, and high patient-to-nurse ratios [45]. One clear consequence of these shortfalls is that neonates receiving supplemental oxygen therapy have prolonged periods with inappropriate SpO_2 levels [46], likely contributing to adverse preterm outcomes, including by example ROP, the incidence of which is clearly rising in low- and middle-income countries [47,48].

At first glance, it would seem that provision of blended oxygen and continuous (rather than absent or intermittent) SpO_2 monitoring would be the priorities for improvement of oxygen supplementation in low resource settings. However the paucity of skilled bedside staff would suggest that even with these in place, optimal SpO_2 targeting is far from assured, thus providing a strong rationale for prioritising automation of oxygen titration from the outset. Successful implementation of automated oxygen control in these circumstances will require adaptation of currently available respiratory support devices, in which blended oxygen is delivered by manual titration of oxygen and air through flow regulators [49]. Actuation of FiO_2 alterations with these devices will hence require software-controlled servomotors, analogous to the FiO_2 actuation system used in the initial clinical studies of the OxyGenie algorithm [26,27]. The characteristics of the adapted blending systems, in particular the time delays associated with full equilibration after an FiO_2 adjustment [50], will need to be taken into account in applying the algorithm safely. The algorithm will need to be partnered with

low-cost pulse oximeters that adhere to WHO device design specifications [51]. An automated oxygen control system of this form is currently being integrated into two low-cost CPAP devices by one of the authors (LMcL), and field tests of the function of this device in preterm infants are planned.

CONCLUSION

The emerging evidence would suggest that automated control of oxygen titration is very likely to become part of routine care for preterm infants, even if clinical trials were to find only marginal clinical benefits beyond tighter control of oxygenation. Assuming no harms are uncovered, the advantages of the technology, especially a rapid response to protracted and profound SpO_2 deviations, will recommend it in the clinical arena. The remaining technical challenges, especially those of individualisation of performance and adaptation to the low-resource setting, should be set as priorities in the quest to optimise oxygen therapy for preterm infants globally.

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Conflict of interest:

The University of Tasmania and Royal Hobart Hospital have jointly lodged a provisional patent application concerning automated control of inspired oxygen concentration in the newborn infant, and have a licensing agreement with SLE Limited in relation to OxyGenie automated oxygen control software. No other competing interests are declared.

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TABLES

Algorithm name [reference]	Algorithm type	Respiratory support device
CliO_2 [12]	Hybrid rule-based and proportional derivative	Avea ventilator (Vyaire Medical, Chicago, USA)
CLAC [13]	Rule-based	Leoni ventilator (Löwenstein Medical SE & Co. KG, Bad Ems, Germany)
PRICO [14]	Rule-based	Fabian ventilator (Vyaire Medical, Chicago, USA)
OxyGenie [15]	Proportional-integral-derivative	SLE6000 ventilator (SLE Limited, South Croydon, UK)
SPOC [16]	Proportional-integral-derivative	Stephan ventilators (Fritz Stephan GMBH, Gackenbach, Germany)
IntellO_2 [17]	Proportional-integral-derivative	Vapotherm nasal high flow device (Vapotherm, Exeter, USA)

Table 1 Contemporary oxygen control algorithms embedded in commercially-available respiratory support devices

FIGURES

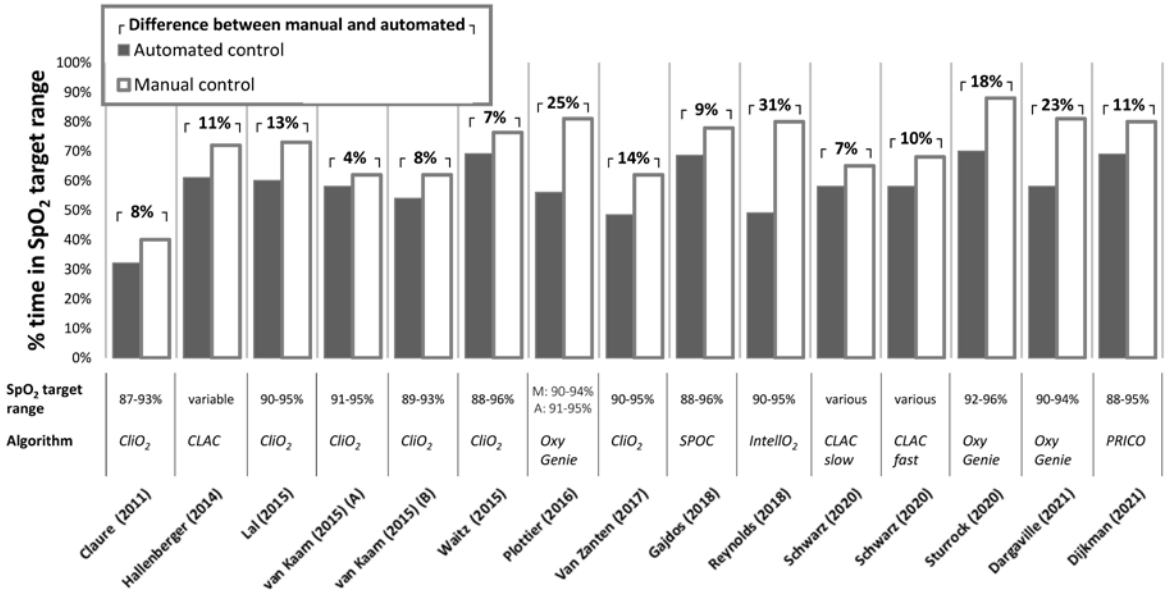

Figure 1. Contemporary crossover studies comparing automated oxygen control with manual control in preterm infants

See text and Table 1 for further details of the crossover studies and oxygen control algorithms. M: manual oxygen control; A: automated oxygen control.

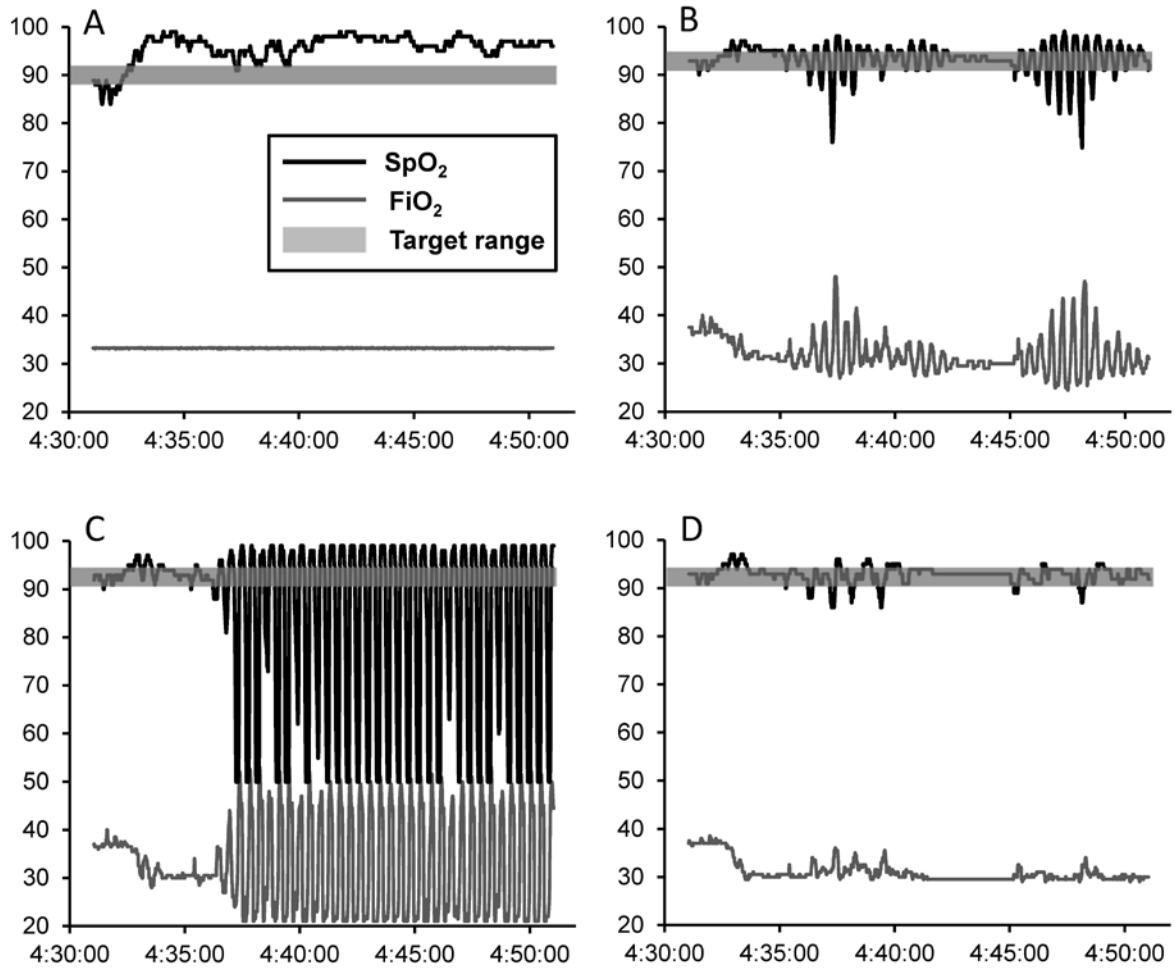

Figure 2. Examples of destabilisation of oxygenation with ill-suited control algorithms

Sample 20 min recordings of SpO_2 (black line, Y-axis: % saturation) and FiO_2 (grey line, Y-axis: % oxygen). Gray band = SpO_2 target range. Panel A: data recording from an infant born at 24 weeks gestation, day 29, on high flow nasal cannula, SpO_2 target range 88-92%. No FiO_2 adjustment made, SpO_2 initially in hypoxaemic range, then fluctuating above target range. Panels B-D: *in silico* simulation of automated oxygen control with different algorithms, using abstracted data from the recordings in panel A. Panels B and C: Examples of SpO_2 instability with a basic PID algorithm (panel B) and with an enhanced PID algorithm without adaptation (panel C). In both cases oscillation in SpO_2 with ~15 second periodicity is noted, induced by immoderate FiO_2 adjustments. Panel D: Oxygen control with an adaptive PID algorithm, resulting in satisfactory SpO_2 control in simulation, without instability. PID: proportional-integral-derivative. Redrawn from reference [15] (online Figure 2), with permission.