Development and pre-clinical testing of an adaptive algorithm for automated control of inspired oxygen in the preterm infant

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SUPPLEMENTAL TEXT

Evaluation of algorithm performance using a simulation of oxygenation

The oxygenation simulator used for algorithm evaluation was developed under the premise that disturbances in oxygenation in preterm infants can be modelled in real-time as a series of paired values for ventilation-perfusion ($\dot{V}/Q$) ratio and shunt (Q_s/Q_t). Thus a continuous recording of FiO_2 and SpO_2 values from a preterm infant was converted second by second to a datastream of $\dot{V}/Q$ and shunt values. In achieving this conversion, the following assumptions were made: 1) that the fundamental oxygenation disturbance determining the baseline oxygen requirement in a given infant was that of $\dot{V}/Q$ mismatch, with a small shunt component (0.1),[1] 2) that the basal oxygen requirement (and thus $\dot{V}/Q$ ratio) would under most circumstances change relatively slowly, and could be re-evaluated on an hourly basis, 3) that the second by second vicissitudes in SpO_2 (in particular significant hypoxaemic events) were the result of alterations in the degree of shunt,[2,3] and 4) that full equilibration to a new steady state of oxygenation would require 30 sec after an FiO_2 adjustment occurred (time delay 10 sec, time constant ~7 sec).[4]

The simulation was programmed in LabVIEW 2010 (National Instruments), and is represented diagrammatically in Online Figure 1. The FiO_2 and SpO_2 data were sourced from a representative daylong recording from each of sixteen preterm infants requiring non-invasive respiratory support and supplemental oxygen therapy.[5] Ethical approval to obtain these recordings was granted by our institutional Human Research Ethics Committee. SpO_2 target range was 88-92%. For the purposes of the simulation, missing SpO_2 values were removed. The basal oxygen requirement was determined for each hour of the recording by isolation of segments in which SpO_2 was within the target range; basal FiO_2 was then determined as the mean FiO_2 from amongst these segments. From this basal FiO_2, in combination with the mid-point of the SpO_2 target range (90%), an unchanging value for $\dot{V}/Q$ was derived for each hour of the recording using standard formulae,[6] and assuming a residual shunt fraction of 0.1. Values for shunt could now be determined second by second by combining the individual SpO_2 and FiO_2 values with the $\dot{V}/Q$ ratio, producing a 1 Hz datastream of $\dot{V}/Q$ and shunt values (the "proxylog"). For this calculation, and that which follows, the relevant value of FiO_2 was taken to be the value 30 sec upstream from (i.e. before) present.

Evaluation of algorithm function could then proceed by linking the proxylog with the FiO_2 output from the algorithm within the automated oxygen controller. During each 1 sec iteration, the relevant FiO_2 from the algorithm under test was combined with the incoming values for $\dot{V}/Q$ and shunt, and a new value of SpO_2 thus determined, logged and input back to the control algorithm to close the feedback control loop. Of note the derived SpO_2 values were potentially very different to that of the original recording from which the proxylog was derived, and it was possible to simulate the targeting of a different SpO_2 range to that originally used.

Using the above simulation and the proxylog from each of the 16 recordings, the performance of all permutations of core PID with SC, K_p adaptation and TRA was evaluated, with the SpO_2 target range set at 91-95%. Function of the core algorithm without an integral term (i.e. PD only), and of the fully-enhanced algorithm with a 30 sec lockout after an FiO_2 adjustment were also examined. For these latter analyses, multiple permutations of PID coefficients were trialled in an attempt to optimise performance.

Validation of the simulation

The software for generating the proxylog was internally validated by re-combining the $\dot{V}/Q$ and shunt values from the proxylog with the original FiO_2 used, with the expectation that the output SpO_2 values would be the same or very similar to those of the original data recording. This was found to be the case, with very high correlation between original and derived SpO_2 values (R=0.99).

A form of external validation of the simulation was undertaken using data from the clinical study described in the companion paper,[7] in which FiO_2 and SpO_2 were recorded at 1 Hz in preterm infants (n=20) during two 4 h periods of manual oxygen control (~8 h of pooled data) and a 4 h period of automated oxygen control using the enhanced PID algorithm described in the main paper. The data from recordings during manual control were converted to a proxylog using a) the "blended $\dot{V}/Q$ and shunt" approach described above, with $\dot{V}/Q$ being a reflection of baseline oxygen requirement (re-evaluated hourly) and shunt changes mirroring the second by second SpO_2 variations, b) a "$\dot{V}/Q$-matched" assumption, in which $\dot{V}/Q$ was fixed at a high value (0.8) and shunt changes alone were assumed to be the cause of oxygenation disturbances, and c) a "zero shunt" assumption, in which $\dot{V}/Q$ changes alone

were held responsible for SpO_2 variability. The proxylog files generated using these 3 approaches were linked in simulation with the enhanced PID algorithm used in the clinical study, allowing the simulated function of the algorithm to be examined and compared, and also compared with the actual data obtained for each of the 20 infants under conditions of automated control using the same algorithm. The actual automated SpO_2 histograms were compared with the "virtual" histograms, and indices of SpO_2 targeting (eupoxia time, SpO_2 <85% and SpO_2 >96% in oxygen) were compared between actual and virtual automated control.

Results of the external validation are shown in Online Figures 3 and 4. In pooled SpO_2 data from all 20 infants, the blended $\dot{V}/Q$ mismatch and shunt approach to proxylog generation produced an automated control cumulative SpO_2 histogram very close to that actually observed (Online Figure 3), suggesting this set of assumptions regarding the cause of oxygenation disturbances holds true in reality. A $\dot{V}/Q$-matched assumption produced a cumulative SpO_2 histogram which departed from the actual histogram in both the hypoxaemic and hyperoxaemic zones, and a zero shunt assumption resulted in a right-shifted histogram significantly discrepant from the actual one (Online Figure 3). The blended $\dot{V}/Q$ and shunt assumption also led to indices of SpO_2 targeting in simulation that closely resembled those actually observed in the group of 20 infants during automated control (Online Figure 4), with in this case separation from the $\dot{V}/Q$-matched assumption which resulted in less eupoxia time and more SpO_2 readings <85% and >96% in oxygen than was actually observed during automated control.

The blended $\dot{V}/Q$ and shunt assumption would thus appear to have validity in this simulation of oxygenation, producing a virtual SpO_2 targeting profile very similar to that actually

observed in preterm infants when linked to the same oxygen control algorithm. Simulations assuming minimal V̇/Q mismatch or no shunt produced SpO_2 targeting profiles that were in several ways unlike the actual profile of automated oxygen control.

Clearly this form of validation has the limitation that the parameters used in the model, V̇/Q and shunt, are not being measured in actual subjects. Invasive measurement of such parameters of oxygenation for long periods is not currently feasible in preterm infants. Such measurements would certainly aid in more fully understanding of the relative contributions of V̇/Q and shunt to the oxygenation disturbances that occur second by second in preterm infants.

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