

## REGULAR ARTICLE

# A randomised controlled trial of an automated oxygen delivery algorithm for preterm neonates receiving supplemental oxygen without mechanical ventilation

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## Keywords

Auto-mixer, Extremely low birth weight infants, Oxygen administration, Oxygen saturation targets, Pulse oximeter

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## ABSTRACT

**Aim:** Providing consistent levels of oxygen saturation (SpO<sub>2</sub>) for infants in neonatal intensive care units is not easy. This study explored how effectively the Auto-Mixer<sup>®</sup> algorithm automatically adjusted fraction of inspired oxygen (FiO<sub>2</sub>) levels to maintain SpO<sub>2</sub> within an intended range in extremely low birth weight infants receiving supplemental oxygen without mechanical ventilation.

**Methods:** Twenty extremely low birth weight infants were randomly assigned to the Auto-Mixer<sup>®</sup> group or the manual intervention group and studied for 12 h. The SpO<sub>2</sub> target was 85–93%, and the outcomes were the percentage of time SpO<sub>2</sub> was within target, SpO<sub>2</sub> variability, SpO<sub>2</sub> >95%, oxygen received and manual interventions.

**Results:** The percentage of time within intended SpO<sub>2</sub> was 58 ± 4% in the Auto-Mixer<sup>®</sup> group and 33.7 ± 4.7% in the manual group, SpO<sub>2</sub> >95% was 26.5% vs 54.8%, average SpO<sub>2</sub> and FiO<sub>2</sub> were 89.8% vs 92.2% and 37% vs 44.1%, and manual interventions were 0 vs 80 (p < 0.05). Brief periods of SpO<sub>2</sub> < 85% occurred more frequently in the Auto-Mixer<sup>®</sup> group.

**Conclusion:** The Auto-Mixer<sup>®</sup> effectively increased the percentage of time that SpO<sub>2</sub> was within the intended target range and decreased the time with high SpO<sub>2</sub> in spontaneously breathing extremely low birth weight infants receiving supplemental oxygen.

## INTRODUCTION

Oxygen has been used in neonatal intensive care units (NICUs) since the 1940s, and its application was later associated with retinopathy of prematurity (ROP) (1–3). Pulse oximeters that monitor oxygen saturation (SpO<sub>2</sub>) have been routinely used in most NICUs since the 1980s to guide manual adjustments of the fraction of inspired oxygen (FiO<sub>2</sub>). However, manually controlling FiO<sub>2</sub> is often time-consuming and untimely in preterm infants, which increases the risks of associated side effects affecting the eyes, lungs and central nervous system (4–6). Retinopathy of prematurity is the most important cause of blindness in the city of Cali, Colombia, (7) and accounts for 34% of all blind children in the city.

Despite recently published randomised trials (8–11), we still do not know what the ideal SpO<sub>2</sub> target is for all infants. In extremely low birth weight infants, it seems prudent not to use SpO<sub>2</sub> targets of 85–89% and to avoid

SpO<sub>2</sub> above 94%, as it has been reported that the partial pressure of oxygen dissolved in arterial blood was >80 mmHg in 60% of the samples (12). With wide SpO<sub>2</sub> targets that aim to avoid hyperoxia in very low birth weight infants, neonatal morbidity is decreased without a negative effect on mortality or in follow-up (13–18). However, the time spent outside targeted ranges could be high. According to one study performed in infants <28 weeks' gestation (19), there was significant intercentre variability between

## Abbreviations

CPAP, Continuous positive airway pressure; FiO<sub>2</sub>, Fraction of inspired oxygen; NICUs, Neonatal intensive care units; ROP, Retinopathy of prematurity; SpO<sub>2</sub>, Oxygen saturation.

## Key notes

- Providing consistent levels of oxygen saturation (SpO<sub>2</sub>) for extremely low birth weight infants is not easy.
- This study explored how well the Auto-Mixer<sup>®</sup> algorithm automatically adjusted fraction of inspired oxygen levels to maintain SpO<sub>2</sub> within an intended range in infants receiving supplemental oxygen without mechanical ventilation.
- The Auto-Mixer<sup>®</sup> effectively increased the percentage of time that SpO<sub>2</sub> was within the intended target range and decreased the time with high SpO<sub>2</sub>.

intended and actual SpO<sub>2</sub> values, with SpO<sub>2</sub> levels being above the intended target 30–76% of the time.

In order to decrease adverse effects related to oxygen, the SpO<sub>2</sub> and the FiO<sub>2</sub> have to be carefully controlled to minimise exposure to hypoxaemia and hyperoxaemia and to significant fluctuation between the two conditions (20). However, SpO<sub>2</sub> technology is complex, there are significant differences between SpO<sub>2</sub> monitors, and oxygen administration depends completely on the availability, knowledge and experience of the healthcare staff providing the care. Details of systems that can automatically modify FiO<sub>2</sub> in infants being mechanically ventilated have been published (21–25), but we still need to assess the efficacy of automated FiO<sub>2</sub> adjustment for infants in more stable conditions, who require less-invasive respiratory support (23).

The research group at the Centro Médico Imbanaco in Cali, Colombia, has designed and developed the Auto-Mixer<sup>®</sup> algorithm, which automatically controls oxygen administration for infants without mechanical ventilation (26). The aim of this proof-of-concept randomised controlled clinical trial was to determine the efficacy of the Auto-Mixer<sup>®</sup> algorithm, by measuring how it automatically adjusted FiO<sub>2</sub> levels to maintain SpO<sub>2</sub> within an intended range in preterm infants receiving supplemental oxygen without mechanical ventilation.

## METHODS

### Automated FiO<sub>2</sub> system

The Auto-Mixer<sup>®</sup> algorithm (Centro Médico Imbanaco, Cali, Colombia), which is shown in Figure 1, analyses the infant's SpO<sub>2</sub>, using a monitor with signal extraction technology that automatically identifies motion-associated artefacts and excludes them from analysis (model Rad-9; Masimo Corporation, Irvine, Ca, USA). The Auto-Mixer<sup>®</sup> then automatically regulates the FiO<sub>2</sub> to be administered to the infant, in response to the SpO<sub>2</sub> input and the treatment objectives specified by the clinician.

A detailed description of the algorithm has been recently published (26). This study summarises the most salient points.

The Auto-Mixer<sup>®</sup> algorithm was designed to continuously sense, monitor and process the infant's SpO<sub>2</sub> signal



**Figure 1** The Auto-Mixer.

from the Masimo monitor and not to respond immediately to sudden and brief falls in SpO<sub>2</sub>. The SpO<sub>2</sub> signals obtained from a serial port in the monitor are interpreted, stored and digitally processed in an electronic circuit ruled by a microcontroller. This microcontroller then transmits the data, receives the desired parameters set by the user and executes the control actions on the blender. The logic that governs FiO<sub>2</sub> adjustments is based on a microprocessor that uses diffuse logic control techniques.

The Auto-Mixer<sup>®</sup> has an LCD display that allows the user to see the parameters that have been chosen and how much FiO<sub>2</sub> has been administered. The parameters that can be selected are: (i) the level of FiO<sub>2</sub> at the start of the treatment, (ii) the minimum and maximum SpO<sub>2</sub> limits that the healthcare team considers appropriate for the infant (iii) the amount of time that the operator has chosen to respond to the oxygen value (TO<sub>2</sub> in Fig. 1), ranging from five to 90 sec and (iv) the magnitude of FiO<sub>2</sub> increments and decrements, ranging from 1% to 20%. For this study, we selected SpO<sub>2</sub> limits of 85% and 93%, as this was what was being used in the NICU, but the clinician could choose any other limits. The time chosen to respond to the oxygen value was set at 10 sec, and the magnitude of FiO<sub>2</sub> increments and decrements was set at 1–5%. The microprocessor 'knows' the maximum and minimum limits of SpO<sub>2</sub> that have been selected and increases or decreases the FiO<sub>2</sub> in an attempt to maintain the SpO<sub>2</sub> at, or around, the mean value of the limits chosen. The algorithm's response is directly proportional to the magnitude of the difference between the actual SpO<sub>2</sub> and the desired level. The greater the SpO<sub>2</sub> difference from the mean, the greater the FiO<sub>2</sub> change within the selected magnitude of change selected. Additionally, when SpO<sub>2</sub> remains at, or above, the mean of the chosen limits for at least three minutes, the algorithm reduces the FiO<sub>2</sub> by 2%. If this change reduces the SpO<sub>2</sub> below the mean, the algorithm increases the FiO<sub>2</sub> to the previous value. Finally, the Auto-Mixer<sup>®</sup> has a sound and visual alarm that is activated when the infant is outside the maximum or minimum limit for 40 sec, in case any other complications require immediate action.

### Study design and subjects

This was a proof-of-concept randomised trial to evaluate the Auto-Mixer<sup>®</sup> in extremely low birth weight infants. Infants were included if they were <30 weeks' gestation and <1000 g at birth, receiving supplemental oxygen by nasal cannula and having episodes of desaturation or hypoxaemia. The infants continued to receive oxygen throughout the 12 h of the study. We did not study infants on mechanical ventilation, those who had congenital anomalies or if we did not have parental consent.

We estimated that to detect a 20% difference in the percentage of time spent outside the target range, we would need to analyse 100 h of monitoring and care. This calculation was based on published data (19) on the failure rate to maintain the SpO<sub>2</sub> target within range during routine care and on our own data. We designed the study

to randomly compare the two groups, and randomisation was carried out using sealed envelopes. Fraction of inspired oxygen was manually adjusted in the control group, which is the traditional routine for neonatal care in our NICU, and in the other group, it was controlled by the Auto-Mixer<sup>®</sup>. The evaluation period for all the infants was set at 12 h (720 min), and we planned to randomly include 10 infants in each group, so that we could collect a total of 120 h (7200 min) of data for each group.

Because the study did not interfere with clinical care, the clinicians chose whether to deliver low or high flow gas. We acknowledge that the FiO<sub>2</sub> at the blender is not the same as the one that the infants' lungs receive, being higher in varying degrees at the blender. The SpO<sub>2</sub> target range (85–93%) and the alarm settings (low 84% and high 94%) were the ones that were usually used in the NICU. The primary outcome was the percentage of time that SpO<sub>2</sub> was within the desired target range, and the secondary outcomes were nursing interventions, the amount of oxygen received by the infant during the study period and the variability of SpO<sub>2</sub>.

Oxygen saturation was continuously measured in each infant using the monitor with signal extraction technology, mentioned earlier in this study, which could automatically identify motion-associated SpO<sub>2</sub> artefacts and exclude them from analysis. In the control group, the bedside healthcare providers manually adjusted the FiO<sub>2</sub> in line with our standard NICU practice. A respiratory therapist researcher checked that all the manual changes were recorded. In the treatment group, the SpO<sub>2</sub> values were received by the Auto-Mixer<sup>®</sup>, which adjusted the FiO<sub>2</sub> as previously described. During the 12-h period of the study, we recorded the SpO<sub>2</sub> and FiO<sub>2</sub> values for each infant in real time, using a computer set-up for this purpose.

The study was approved by the Ethics Committee at Centro Médico Imbanaco in Cali, Colombia, in line with regulatory guidelines from the Ministry of Health of Colombia and the World Principles of Ethics described in the Declaration of Helsinki (revised October 2008).

The neonatal respiratory therapist hired to monitor the trial explained the aim of the study to the parents, and they read the informed consent together. They were reassured that the study was only designed to evaluate the performance of the Auto-Mixer<sup>®</sup> for 12 h and that this would change the care their infant received. All the study infants were supervised by the respiratory therapist, and the parents were told that there would be no clinical intervention unless any adverse effects were noted with the Auto-Mixer<sup>®</sup>. The respiratory therapist also ensured that all the equipment – the SpO<sub>2</sub> monitors, sensors and Auto-Mixer<sup>®</sup> computer – were functioning adequately and registered all manual interventions on the blender performed by bedside healthcare providers.

### Statistical methods

Data were analysed using software SPSS version 19 using descriptive statistics and variability measures to analyse SpO<sub>2</sub> dispersion outside the selected range. The Levene's

test was utilised to analyse the homogeneity of the variances, and ANOVA was used for comparisons between groups. Statistical significance was set at  $p < 0.05$ .

### RESULTS

The study was performed over 11 months in 2011, and 28 newborn infants were eligible to take part. Of these, 20 receiving supplemental oxygen, but not through mechanical ventilation, were included. Eight were not included, three because their parents refused consent and five because investigators were not available. Ten infants were randomised to each group and completed the 12-h study period. There were no significant differences between the groups in mean gestational age ( $27.3 \pm 1.7$  vs  $27.7 \pm 1.7$  weeks) and birth weight ( $785 \pm 47.7$  vs  $763 \pm 45.8$  g). Postnatal age at the time of the study varied from five to 14 days, as some infants who met the inclusion criteria had previously been on mechanical ventilation, continuous positive airway pressure, oxygen by nasal cannula or no oxygen. The median age was not different between the groups, at 9 days in the manual control group and 8 days in the Auto-Mixer<sup>®</sup> group. All the infants had experienced at least two daily episodes of hypoxaemia and desaturation before randomisation, ranging from two to 12, with a median of six in both groups, and the episodes of clinically suspected or laboratory confirmed infection were the same (30%). The number of babies receiving high flow oxygen by nasal cannula was similar, with six in the manual control group and five in the Auto-Mixer<sup>®</sup> group. As this was a short study of only 12 h, we did not collect any long-term hospital or postdischarge data. We recorded data for 720 min for each infant, and this provided 7200 min on the 10 infants with routine manual adjustments and 7200 min on the 10 newborns in the Auto-Mixer<sup>®</sup> group. We were able to obtain a total of 57 087 reliable data points in the 20 infants: 32 621 in the Auto-Mixer<sup>®</sup> group and 24 466 in the manual control group. As explained in the methods section, these were due to the fact that, by design, we excluded motion-associated or other SpO<sub>2</sub> artefacts. There were also data dropouts, either due to periods of care and/or changes of sensor site.

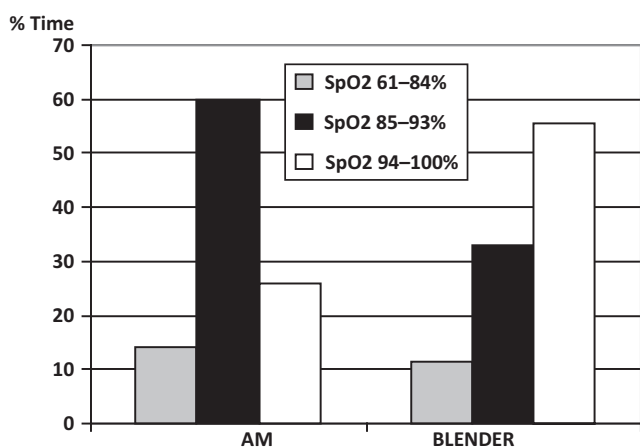
Table 1 shows the percentage of time that SpO<sub>2</sub> was maintained within the intended target, the percentage of time that SpO<sub>2</sub> exceeded 95%, the average SpO<sub>2</sub> and FiO<sub>2</sub> over the 12-h period and SpO<sub>2</sub> variability. The differences were statistically significant between the two groups, and SpO<sub>2</sub> varied less in the automatic group. The variance in all these findings were detected using Levene's test, with  $p = 0.0001$ . This confirms that the difference in FiO<sub>2</sub> administration between the two methods was genuinely statistically different and not just due to random chance.

The Auto-Mixer<sup>®</sup> made 7540 automatic FiO<sub>2</sub> adjustments during the 12-h period, and the staff made a significantly lower 80 manual oxygen adjustments in the control group and none in the Auto-Mixer<sup>®</sup> group (Table 1).

Figure 2 shows the comparisons of the percentages of time spent within, below and above the intended SpO<sub>2</sub>

**Table 1** Oxygen control over the 120 h in the two groups receiving noninvasive oxygen therapy

	Auto-Mixer	Blender-manual routine care	p-value
Percentage of time with SpO <sub>2</sub> maintained within target	58 ± 4%	33.7 ± 4.7%	<0.01
Percentage of time with SpO <sub>2</sub> >95%	26.5%	54.8%	<0.01
12-h SpO <sub>2</sub> (%)	89.8	92.2	<0.05
SpO <sub>2</sub> variability (%)	5.7	6.3	<0.05
12-h FiO <sub>2</sub> (%)	37	44	<0.01
Manual interventions	0	80	<0.001

SpO<sub>2</sub>, Oxygen saturation.**Figure 2** Percentage of time spent below, within and above the intended oxygen saturation (SpO<sub>2</sub>) range with the Auto-Mixer (AM) and manual routine care (blender).

range. The percentage of time within range was significantly higher in the Auto-Mixer<sup>®</sup> than in manual care group, and the time above range was significantly lower ( $p < 0.05$ ). The manual control group spent more time above the intended SpO<sub>2</sub> maximum limit, and the most frequent SpO<sub>2</sub> values were 96–98%, statistically different from the Auto-Mixer<sup>®</sup> group. At the lower end of SpO<sub>2</sub>, the percentage of time with SpO<sub>2</sub> under 85% was higher in the automatic group (14%) than the manual group (11%) ( $p = 0.05$ ). We have information on the frequency of each SpO<sub>2</sub> value in 1% increments in both groups, but these data are not shown graphically. There was an overall increased frequency of SpO<sub>2</sub> values of 80–85% in the Auto-Mixer<sup>®</sup> group, but these were of shorter duration, at a median of 7 sec, than the 15 sec in the manual control group. Furthermore, SpO<sub>2</sub> values of 80–85% that lasted more than 30 sec, and the frequency of SpO<sub>2</sub> values of 70–75% were higher in the manual control group.

## DISCUSSION

This paper presents a clinical evaluation of the Auto-Mixer<sup>®</sup> algorithm, which was specifically developed to automatically control FiO<sub>2</sub> in preterm infants receiving noninvasive respiratory support and supplemental oxygen. It is based on new-generation, motion-resistant pulse oximetry that can automatically identify motion-associated SpO<sub>2</sub> artefacts and exclude them from analysis. The results of this study show that using the Auto-Mixer<sup>®</sup> improved the proportion of time that infants spent within with SpO<sub>2</sub> target, showed less SpO<sub>2</sub> variability than the manually controlled method and resulted in NICU staff spending less time manually adjusting FiO<sub>2</sub>. In addition, the algorithm reduced the percentage of time when SpO<sub>2</sub> was over 95%, thereby reducing the frequency and duration of hyperoxic episodes. These data, obtained under routine NICU conditions, suggest that the Auto-Mixer<sup>®</sup> FiO<sub>2</sub> controller improves oxygen administration to preterm infants not on mechanical ventilation, while reducing staff workload.

Despite recently published randomised studies (8–11), the best oxygen profiles to reduce ROP, while optimising preterm infant health and development, remain unknown (27). Periods of hyperoxaemia, and the extent of fluctuations in blood oxygen tension, affect the initiation and progression of ROP (28–31). Both hypoxaemia and hyperoxaemia occur frequently in clinical practice during routine manual FiO<sub>2</sub> control, suggesting that differences in clinical practice may account for different incidences of ROP. This is a global problem of different magnitude in different units. Finding out how to increase the percentage of time spent within intended SpO<sub>2</sub> targets and diminishing wide SpO<sub>2</sub> fluctuations could be advantageous to neonatal care and outcomes. The Auto-Mixer<sup>®</sup> proved effective at doing that in spontaneously breathing infants. The clinical high and low SpO<sub>2</sub> limits can be freely configured with this FiO<sub>2</sub> controller software and can therefore be adapted to any clinical targets.

Several studies have tested different automatic FiO<sub>2</sub> control systems (21–23) and compared routine optimal manual adjustments and automatic control in ventilated infants. The present study used a different algorithm and was carried out in infants receiving oxygen and not mechanical ventilation.

As described in the results, using the algorithm increased the percentage of time with SpO<sub>2</sub> of <85%, an increase that has been noted in studies with other equipment. In this study, the episodes of SpO<sub>2</sub> 80–85% in the algorithm group occurred more frequently but were shorter than those in the manual control group. Furthermore, prolonged episodes with automated FiO<sub>2</sub> adjustment were less frequent, and the number of episodes of more significant hypoxaemia (SpO<sub>2</sub> 70–75%) were less frequent in the algorithm than manual control group. The impact of frequency and duration on desaturation is currently being investigated. It is not clearly known whether frequent but brief desaturations are more detrimental than less frequent, prolonged desaturations, but

the severity of hypoxaemia, with lower SpO<sub>2</sub> values during desaturations, is likely to have a worse impact.

It has been shown that maintaining higher basal SpO<sub>2</sub> values is an effective way of reducing episodes of decreased SpO<sub>2</sub>, but at a cost of increased oxygen exposure (32). Preventing or decreasing episodes of SpO<sub>2</sub> 80–85% can be achieved using the algorithm in different ways. One is setting a higher SpO<sub>2</sub> value for the low limit. Another is providing higher FiO<sub>2</sub> and/or tolerating higher SpO<sub>2</sub> values, but this may be associated with more time exposed to hyperoxia, with its associated severe risks. Although selecting FiO<sub>2</sub> increments higher than the 1–5% used in this study may prove useful, this was not evaluated. However, increasing FiO<sub>2</sub> rapidly, and by greater amounts in response to short events, may be inappropriate and could increase the risk over overshooting and increasing the frequency of SpO<sub>2</sub> fluctuations. For this reason, the algorithm was designed to not to respond immediately to sudden and brief falls in SpO<sub>2</sub>. Manual care intervention may be a solution in such cases, such as changing the infant's position, reconnecting the tube or stimulation in the case of apnoea. Automated FiO<sub>2</sub> adjustment should never be a substitute for close and mandatory clinical supervision and more appropriate interventions based on the clinical assessment of each individual situation in each individual baby.

In our study, 55% of the SpO<sub>2</sub> values were more than 93% in the control group, which is similar to the 36–70% reported by other studies, which included infants on mechanical ventilation, for the proportion of time with saturations over the target range (19,23). Greater intercentre variability in achieved versus intended pulse oximeter saturation has also been described (19). The precision targeting of SpO<sub>2</sub> in preterm infants on continuous positive airway pressure (CPAP) was reported, for the first time, by Lim et al. (33). When they required supplemental oxygen, these infants were outside the target SpO<sub>2</sub> range for 69% of the total recording time and had 48 episodes of severe hyperoxia (SpO<sub>2</sub> >98%) in 24 h (33). In another recent study, where the prevalence of ROP was reduced, without increasing mortality, using SpO<sub>2</sub> targets of 85–93%, the data showed that some infants spent at least 50% of the 24-h period above that range (34). These recent studies (33–35) are comparable to the findings in the control group in our current study. Furthermore, FiO<sub>2</sub> was adjusted an average of 25 times per day and, when each nurse was caring for more patients, the frequency of prolonged hyperoxia increased (33).

This study had some limitations. It is very difficult to mask a study like this and, by design, this study was not masked. However, all the recorded data were analysed without the participation of the investigators. In addition, we followed routine NICU procedures for clinical care, oxygen administration, SpO<sub>2</sub> targets and the nursing to patient ratio. Altering this may have modified the percentage of time that infants spent within the intended SpO<sub>2</sub> target and with SpO<sub>2</sub> >95%. The strength of the study, on the other hand, is that it is a randomised study comparing a newly developed tool in extremely low birth weight infants,

who are receiving oxygen but are not on mechanical ventilation.

## CONCLUSIONS

This randomised study was carried out under routine NICU conditions in preterm infants, who were breathing spontaneously, required oxygen and demonstrated frequent fluctuations in SpO<sub>2</sub>. It showed that when FiO<sub>2</sub> was adjusted automatically, the intended SpO<sub>2</sub> target was better maintained, and there was less exposure to high SpO<sub>2</sub> values. At the same time, the Auto-Mixer<sup>®</sup> algorithm reduced FiO<sub>2</sub> requirements and the need for staff intervention, compensating for some of the limitations that presently exist with conventional forms of noninvasive oxygen administration. These effects were accompanied by more frequent, but shorter-lived, episodes that increased the overall percentage of time with SpO<sub>2</sub> at 80–85%. We believe that the automatic control algorithm used in this study is cost-effective and may decrease the rates of neonatal conditions and morbidities associated with unnecessarily high exposure to oxygen, large fluctuations in oxygen levels, hyperoxaemia and increased radical oxygen species. These reductions are of benefit to the individual infant, their family and society as a whole. Further research is needed to determine the algorithm's impact on the long-term respiratory, ophthalmic and neurologic outcomes of preterm infants.

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## CONFLICTS OF INTEREST

The Auto-Mixer<sup>®</sup> algorithm for the automated adjustment of FIO<sub>2</sub> was developed in Cali, Colombia, and patented by James Zapata, Robinson Araque Campo and Alejandro Matiz Rubio, who also hold the intellectual rights. Augusto Sola became a part-time employee at the Masimo Corporation, Irvine, California, USA, which produces the signal extraction technology used by the Auto-Mixer<sup>®</sup>, in January 2013, after the work in this paper was completed. No author or individual received an honorarium, grant or other form of payment to produce the manuscript.

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