



## Controversies about the resuscitation of extremely preterm infants in the delivery room

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### Abstract

**Objective:** To describe the main controversies about resuscitation procedures performed in extremely low birth weight infants in the delivery room.

**Sources of data:** Systematic review including articles from MEDLINE, SciELO and Cochrane Library, and abstracts published in national and international proceedings, using the keywords resuscitation, asphyxia, and newborn infant.

**Summary of the findings:** The main controversies concern the oxygenation and ventilation of extremely low birth weight infants. The effects of oxygen concentrations between 21 and 100% need to be addressed. Appropriate inspiratory pressure, lung volume, and positive end-expiratory pressure parameters also need to be established in order to decrease barotrauma and volutrauma. The benefits of nasal continuous positive airway pressure may be determined through randomized clinical trials. On top of that, manual resuscitation devices have to be developed in order to optimize these ventilatory parameters and to reduce lung injury. So far, clinical trials on the administration of epinephrine, volume expanders, and sodium bicarbonate to extremely low birth weight infants have not been published. In addition, the main ethical dilemma concerns the decision of health professionals and parents not to initiate resuscitation procedures at very low gestational ages.

**Conclusions:** In the future, guidelines may be modified based on the results of randomized and controlled clinical trials, as well as neurodevelopmental follow-up studies, involving extremely low birth weight infants submitted to resuscitation procedures in the delivery room.

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### Introduction

Adequate care to newborn infants in the delivery room is essential so as to prevent asphyxial lesions, which cause neonatal death, and neurological sequelae in those who survive, impairing their quality of life and of their families as well.

In February 2000, the committees for neonatal resuscitation of the American Academy of Pediatrics, of the International Committee on Resuscitation (Europe, Canada, Australia, New Zealand, South Africa, Latin America), of the American Heart Association and of the World Health Organization developed guidelines for the recommendation and use of the most efficient resuscitation procedures based on research data, knowledge and experience. The recommended practices were then published in scientific articles and in the Textbook of Neonatal Resuscitation in 2000<sup>1,2</sup> and have been taught through the Neonatal Resuscitation Program of the Brazilian Society of Pediatrics at a nationwide level.

Nevertheless, despite the wide use of these procedures, some of them have been performed based on clinical experience and on animal and adult studies. Thus, there is controversy over their use in full-term newborn infants<sup>3</sup> and mainly in very low birthweight infants, especially in extremely

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low birthweight ones, i.e., those weighing less than 1,000 g at birth.<sup>4</sup> Infants with such a birthweight correspond to the 95th percentile of a 22-week gestation, to the 50th percentile of a 27-week gestation and to the 10th percentile of a 30-week gestation.<sup>5</sup> Thus, this article aims to discuss the main controversial issues related to the resuscitation of extremely preterm infants in the delivery room.

At present time, the procedures carried out during neonatal resuscitation include: - maintaining the body temperature by way of heat treatment; - maintaining airway permeability through correct head and neck positioning; aspiration of the mouth, nose and, if necessary, of the trachea; - mechanical ventilation using positive air pressure with a balloon and mask or balloon and tracheal tube; - maintaining circulation by applying cardiopulmonary resuscitation and administering drugs or fluids. All these procedures are performed based on integrated evaluation of three signs: breathing, heart rate and color.<sup>1,2</sup>

### **Maintenance of body temperature**

The first step to be taken in the delivery room is to maintain the newborn's body temperature by using warm fields and radiant heat. The drying process prevents heat loss from evaporation and conduction and is also a tactile stimulus to the onset of breathing.<sup>1,2</sup>

Preterm infants are highly susceptible to cold stress, since their ratio between body area and weight is large, which results in hypothermia, hypoxemia and acidosis. To reduce heat loss in those weighing less than 1,000g, a transparent PVC film has been used. After drying them with warm fields under radiant heat, the infant can be totally wrapped in PVC, except the face, and then resuscitation maneuvers can be applied.<sup>6</sup> In addition, it has been shown that in case of patients with 23 to 27 weeks of gestational age, wrapping only the trunk and limbs in a polyethylene bag (20 x 50 cm) immediately after birth, without previous drying, under radiant heat, reduces heat loss.<sup>7</sup> These practices are inexpensive, easy to use and efficient and do not interfere with resuscitation procedures. On the other hand, special care should be taken in order to avoid hyperthermia since it is associated with respiratory depression.<sup>8,9</sup>

A study conducted in 1998 in 56 Canadian maternity wards showed that hypothermia and hyperthermia are frequent in the delivery room. Neutral temperature could not be obtained in 52% of 520 newborns at the end of resuscitation, so 27% had hypothermia and 25% hyperthermia.<sup>10</sup> As to the prevention of hypothermia (< 36 °C), some institutions have employed radiant heat over the cradles of patients weighing less than 1,500 g or chemically-heated mattresses, whereas others have placed the patients and the mattress inside plastic bags, besides placing caps, which are maintained up to the admission to the neonatal intensive care unit. Multidisciplinary teams of five U.S. neonatal units managed to reduce hypothermia from 40% in 1997-1999 to 15% in 2000-2001<sup>11</sup> by implementing these practices, with the aim of reducing the incidence of peri-intraventricular hemorrhage.

Another aspect related to hypothermia concerns its therapeutic action due to the possible reduction of brain damage in hypoxic-ischemic encephalopathy. With the purpose of verifying whether systemic hypothermia, initiated before six hours of life and maintained for 72 hours, reduces mortality and/or developmental disorders, controlled and randomized clinical trials including full-term newborns with moderate or severe hypothermia are underway. Up to the moment, these publications have only provided data on the safety of the procedure in full-term newborns.<sup>12,13</sup> With regard to its possible application to preterm infants, no studies have been published yet.

### **Airway aspiration**

Immediately after birth, the infant's head is positioned with the neck slightly extended and secretions are aspirated in order to allow for airway permeability. The mouth and then the nostrils are delicately aspirated with a tracheal tube no. 6-8, coupled to a vacuum aspirator, under a maximum negative pressure of 100 mmHg, exercising caution so as to avoid aspirating the larynx, causing laryngeal spasm and vagal bradycardia and delaying the onset of respiration.<sup>1,2</sup> This procedure has not been specifically discussed with regard to preterm infants, however, the neutral position of the head has been a common practice in the first 72 hours of life for the prevention of peri-intraventricular hemorrhage in very low birthweight infants.<sup>11</sup>

### **Oxygenation**

After maintenance of body temperature and airway permeability, if the preterm infant is breathing spontaneously, has a heart rate greater than 100 bpm and central cyanosis, the use of inhaled oxygen is recommended. The oxygen can be provided through a mask with side holes, anesthetic bag or a catheter connected to the source of oxygen at 5 l/min, which has a concentration close to 100%. On top of that, if the newborn has at least one of the following situations: apnea, gasping, heart rate less than 100 bpm or persistent cyanosis, despite receiving inhaled oxygen, pressure-controlled ventilation is indicated. A self-inflating bag with a 750-ml maximum capacity, connected to the source of oxygen at 5 l/min and linked to a reservoir is used to achieve an oxygen concentration of 90 to 100%.<sup>1,2</sup>

The main controversy investigated in the last few years has been the minimum concentration of oxygen necessary to resuscitate a newborn infant at birth. Some authors have argued about the necessity to use an oxygen concentration of 100%, recommended in the routine practice based on studies involving animals and newborn infants.<sup>14,15</sup> This argument results from the concern with the toxic potential of oxygen, which has already been observed in full-term asphyxiated newborns in whom a concentration of 100% was used for resuscitation.<sup>16</sup> After a long period of hypoxia, the tissue level of hypoxanthines is high. When hypoxanthines combine with oxygen in the presence of xanthine-oxidase, a large amount of free

radicals is produced, which may oxidize enzymes, inhibit protein and DNA synthesis, reduce the production of surfactant and cause lipid peroxidation with consequent tissue injury. These oxygen free radicals – superoxide, hydrogen peroxide and hydroxyl – have been implicated in the pathogenesis of several diseases that affect the lungs, brain and other systems of newborn infants, especially preterm ones. Preterm infants are particularly vulnerable to lung injury induced by free radicals, since the antioxidant system develops in the last trimester of pregnancy. This system includes catalase, superoxide-dismutase and glutathione-reductase and free radical scavengers, such as vitamins A, E and C, betacarotene and glutathione, whose levels are low in preterm infants.<sup>17</sup> Therefore, the amount of oxygen free radicals may exceed the antioxidant capacity of preterm infants and cause diffuse lung injury which, if not treated, leads to the development of diffuse alveolar injury and to progressive pulmonary dysfunction. Another concern is with high oxygen pressure in extremely preterm infants and its contribution to the incidence of retinopathy of prematurity.<sup>18</sup>

It is very likely that the low oxygen concentration during neonatal resuscitation will lead to a low production of free radicals and will reduce tissue injury after reperfusion.<sup>19</sup> In the 1960s, experiments with rabbits showed that an increase in arterial oxygen pressure from 50 mmHg to hundreds of mmHg caused little change in pulmonary vasodilation, provided that there was no malformation or lung immaturity, and that room air ventilation was appropriate to ensure alveolar diffusion of oxygen to the bloodstream.<sup>20</sup> In addition, porcine studies show that room air resuscitation decreases vascular pulmonary resistance similarly to that with an oxygen concentration at 100%.<sup>1,22</sup>

The only clinical trial involving newborn infants with gestational age less than 33 weeks assigned to receive ambient air or oxygen during initial stabilization showed a high cerebral blood flow in the first group in the second hour of life. Since PaCO<sub>2</sub> was similar in both groups, exposure to different oxygen concentrations was the only explanation to this finding, although the consequences are unknown.<sup>23</sup>

A meta-analysis of five clinical trials (three open-labeled and two double-blind studies) has been recently published comparing the use of room air with oxygen at 100% in 1,302 newborn infants who needed ventilation, with a mean weight between 2,400 and 3,400 g and a mean gestational age of 37 to 39 weeks.<sup>24</sup> The time elapsed between the infant's crying and the first breath was shorter in room air ventilated patients than in those who received oxygen at 100%. The 5-minute Apgar score was similar in both groups and so was the incidence of hypoxic-ischemic encephalopathy, with the lowest mortality rate at 28 days in patients submitted to room air ventilation; however, the long-term effect could not be determined due to methodological limitations of the study that followed up infants to the age of 12 months.<sup>25</sup> The authors highlight three open-labeled trials carried out in developing countries and the use of oxygen at 100% when

cyanosis and bradycardia did not resolve in 90 seconds, necessary in 168 (27%) of 635 patients who had initially been submitted to room air ventilation.

These authors conclude that room air ventilation may be initially used in full-term or near-term infants with moderate asphyxia, but there always should be spare oxygen in case of resuscitation failure. They underscore that intermediate concentrations have to be investigated in clinical trials that should include preterm infants stratified according to gestational age, with continuous monitoring of oxygen saturation and heart rate using pulse oximetry in the delivery room. Moreover, these studies should include confounding variables, such as cause of respiratory depression, place of birth and available resources.<sup>24</sup> This view is also shared by other researchers.<sup>26-28</sup> These clinical trials are necessary, as a recent investigation showed that half of 40 institutions in 23 countries of five continents use variable oxygen concentrations in the treatment of newborn infants in the delivery room, whereas the remaining 50% have used oxygen at 100%.<sup>29</sup>

From a practical point of view, perhaps the widespread use of pulse oximetry in the delivery room can help to quickly reestablish normoxia and attain normal oxygenation levels throughout the resuscitation process and also after it.<sup>26</sup>

Another relevant issue is the use of cold, sometimes dry, oxygen in the delivery room, which is toxic to the pulmonary epithelium and may cause inflammatory response. Researchers emphasize the current different practices in the delivery room and in intensive care units, where much more attention is paid to the heating and humidification of respiratory gases.<sup>30</sup>

## Ventilation

Besides the concern with the ideal oxygen concentration that should be used for neonatal resuscitation, it is also important to determine the effects of pressure and volume during manual ventilation, especially in extremely preterm infants.

Initially, some aspects of lung mechanics should be considered in case of preterm infants: functional residual capacity established within the first respiratory movements, increase in lung volume and use of positive end-expiratory pressure (PEEP).

Most of the information about functional residual capacity at birth derives from studies involving full-term newborns; however, these concepts can also be applied to preterm infants. Upton & Milner<sup>31</sup> assessed first positive pressure ventilations in 30 asphyxiated newborns using 40 movements/minute with a mean inspiratory time of 0.51 second without PEEP and applying the necessary pressure to obtain ribcage expansion. Of 30 patients, 22 were preterm with a mean birthweight of 1,760 g (range: 580-3,980) and a mean gestational age of 33 weeks (26-42). A mean pressure of 40 cm H<sub>2</sub>O was observed during the first breaths (28-60). Thus, half of the patients required a pressure greater than this value. Ten preterm infants did

not have functional residual capacity at the beginning, but this capacity increased after several insufflations, indicating that an end-expiratory pressure would be necessary to properly establish it, due to surfactant deficiency. Other authors,<sup>32</sup> when ventilating preterm infants during resuscitation, began with an inspiratory pressure of 16 cm H<sub>2</sub>O and increased 2 cm H<sub>2</sub>O in every insufflation at subsequent times. They also prolonged initial insufflation for 2 to 3 seconds, which probably contributed towards the development of functional residual capacity and to an increase in lung compliance. This increase in functional residual capacity was observed before ribcage expansion, denoting that at the end of five breaths, the air volume received by the lung was enough to expand the ribcage using pressures below 30 cm H<sub>2</sub>O.

Currently, there are two ways to initiate positive pressure ventilation at birth. Apparently, the use of lower pressures with prolonged inspiratory time during the first breath is the most appropriate. This preference may be related to the distribution of the inspired volume and to the possible occurrence of lung injury when high pressures are used, since high volumes can lead to partial hyperdistension of the lung parenchyma, mainly in extremely preterm infants.

In neonatal resuscitation, besides establishing the functional residual capacity, it is necessary to provide sufficient tidal volume in order to promote appropriate gas exchange without causing pulmonary hyperdistension. In practice, the parameter used to monitor the inspiratory flow is the ribcage movement; however, it is still unknown how this movement relates to proper alveolar expansion and ideal tidal volume in a lung that is unevenly expanded.<sup>33</sup>

Animal studies suggest that the excessive variation of lung volume or volutrauma can be the major cause of lung injury.<sup>34,35</sup> As ribcage expansion is inversely proportional to gestational age, the risk of volutrauma in extremely preterm infants is greater than in older preterm newborns. Therefore, satisfactory peak inspiratory pressures can produce excessive tidal volumes, hypocapnia and lung injury. This is also a concern from a neurological point of view, since evidence has shown an association between hyperventilation and hypocapnia in preterm infants and abnormal neurological development with occurrence of periventricular leukomalacia and cerebral palsy.<sup>19,36</sup>

Studies with preterm sheep demonstrated that only six manual insufflations of 35 to 40 ml/kg, performed before surfactant administration and before mechanical ventilation, are enough to compromise the efficacy of surfactant replacement. These sheep revealed more lung injury in the histological analysis, more seriously impaired lung mechanics and less gas exchange, compared to those not submitted to manual ventilation at birth.<sup>35</sup> Additionally, there is a concern that manual ventilation at birth in newborns weighing 600 g may provide up to 40 ml/kg and that during the first 5 minutes of life, very low birthweight infants have more than 100 respiratory movements with these high levels of tidal volume.<sup>19</sup>

The increase in lung volume leads to the distension of pulmonary cells, causing an increase in epithelial and

endothelial permeability and cytokine cascade with consequent proinflammatory reaction and deterioration of the lung injury. This also occurs with insufficient ventilation and is especially worrying in extremely preterm infants with surfactant deficiency, who are subjected to a nonhomogeneous lung expansion. Thus, the possibility of providing an appropriate tidal volume is quite limited during neonatal resuscitation, since necessary knowledge and tools have not been currently available.<sup>33</sup>

In practice, some U.S. neonatal units have monitored tidal volume and inspiratory pressure in the delivery room to prevent hyperventilation and have sought to minimize ribcage expansion by using a tidal volume below 7 ml/kg in extremely preterm infants.<sup>11</sup>

In addition to the aspects related to functional residual capacity and tidal volume, some aspects regarding PEEP have to be considered in preterm infants. Some evidence shows that it is important to maintain immature and surfactant-depleted lungs patent with PEEP in order to minimize pulmonary edema and cytokine release and then improve compliance and the response to the surfactant. Studies with very immature rams have shown that the use of any PEEP during neonatal resuscitation produces remarkable improvement in oxygenation. With a PEEP of 8 cm H<sub>2</sub>O the alveolar-arterial oxygen gradient drops 50% within the first 10 minutes after birth with a slight increase in the PaCO<sub>2</sub> or adverse effects on arterial pressure associated with a 25% increase in lung compliance.<sup>37</sup>

Thus, the purpose of using PEEP in the delivery room is to prevent lung collapse during expiration and to establish the functional residual capacity. If PEEP is performed during resuscitation, it may result in quick improvement of oxygen and carbon dioxide levels and in less lung injury, especially in extremely low birthweight infants.

Some authors have recommended the use of nasal continuous positive airway pressure (CPAP) in the delivery room as a way to reduce mechanical ventilation support and the development of bronchopulmonary dysplasia.<sup>6,38-41</sup> In practice, a qualitative survey with 179 U.S. neonatologists showed that 59% used nasal CPAP and PEEP in the delivery room, while 63% used nasal CPAP with anesthetic bag and 27% with self-inflating bag with PEEP valve. The mean PEEP used was 4.7 cm H<sub>2</sub>O (2-10) in preterm infants and 5.3 cm H<sub>2</sub>O (3-10) in full-term newborns.<sup>42</sup>

At present, some institutions have shown that the use of nasal CPAP is feasible and safe when initiated immediately after birth in preterm infants with less than 28-30 weeks of gestational age.<sup>39-41</sup> However, randomized clinical trials are necessary to show the possible benefits, treatment criteria and risks of this therapy.<sup>43</sup> It should be highlighted that the recommendations made in the year 2000<sup>1,2</sup> for the resuscitation of extremely preterm infants do not contemplate the use of PEEP or CPAP in the delivery room. Therefore, until new practices are defined, probably in 2005, the minimum pressure and volume possible must be used to provide appropriate ventilation by continuous observation of ribcage expansion in extremely low birthweight infants.

Aside from the pathophysiological aspects of pulmonary disease in preterm infants, which hinders adequate ventilation at birth, one of the topics that has been widely discussed recently deals with the available material for appropriate neonatal ventilation. No randomized clinical trials exist comparing different pieces of equipment, which currently consist of anesthetic and self-inflating bags,<sup>1,2</sup> commercially available in our setting, the T-tube recommended in Europe<sup>44,45</sup> and the Neopuff<sup>®</sup> infant resuscitator used in Australia and New Zealand.<sup>46</sup>

The characteristics related to the use of self-inflating bags have been questioned, because in spite of automatic re-expansion and ease of use, it is not possible to provide a constant peak inspiratory pressure, as this depends on the force and speed of balloon compression, on the amount of air leakage, especially between face and mask, and on lung compliance. The maximum inspiratory pressure that can be administered is limited by the escape valve activated at 30-40 cm H<sub>2</sub>O in order to avoid barotrauma, an important cause of acute and chronic lung injury in preterm infants. Nevertheless, it has been demonstrated that these valves are activated in a variable pressure gradient. Additionally, self-inflating bags do not provide PEEP and do not allow for an inspiratory time greater than one second.<sup>30</sup>

With regard to anesthetic bags, they have to be connected to a gas supply and a manometer, can provide inspiratory pressure and allow the use of PEEP. However, the applied pressures can vary considerably due to the difficulty in controlling the gas flow and balloon compression simultaneously. The difficulty related to the use of this type of balloon may result in extremely elevated peak inspiratory pressure and PEEP.

Another resuscitator used in the delivery room is the T-tube connected to the face mask or to the tracheal cannula, which has been used in Europe. Insufflation is obtained due to the interruption of air leakage through the ventilation hole by the pressure of the resuscitator's thumb. There is a valve to limit the inspiratory pressure, allowing for prolonged inspiratory time.<sup>44,45</sup> In addition, the Neopuff<sup>®</sup> infant resuscitator, used in Oceania, allows for the use of constant inspiratory pressure and PEEP, which may be adjusted according to the patient's clinical response.<sup>30,46</sup>

Although these resuscitators provide inspiratory pressure, the use of tidal volume depends mainly on the lung compliance that varies over time according to lung expansion. Thus, the great concern with the use of manual resuscitators is related to not knowing the tidal volume provided during ventilation. Maybe different types of manual resuscitators should be developed based on the etiology of breathing difficulty, since extremely preterm infants differ from full-term infants because they have intrinsic pulmonary disease with immaturity and sometimes infection, making it difficult to establish an appropriate lung volume due to low compliance and surfactant deficiency.<sup>30</sup>

These facts can have important clinical implications for the resuscitation of preterm infants in the delivery room. Ideally, volutrauma should be prevented through normalization of functional residual capacity, improvement

of insufflation and pulmonary blood flow, using the least possible ventilatory support to maintain oxygen release into tissues. However, these goals cannot be easily measured at birth.

This way, further studies are necessary to establish the adequate parameters of inspiratory pressure, lung volume and PEEP in order to properly ventilate extremely low birthweight infants. The advantage of using nasal CPAP in the delivery room also has to be determined through randomized clinical trials. Furthermore, manual resuscitators should be developed to optimize the use of these parameters and to minimize lung injury at the beginning of extrauterine life.

### **Tracheal intubation**

Tracheal intubation, in the delivery room, of extremely low birthweight infants is not universally accepted in the literature. German studies compared mortality and morbidity of patients with gestational age above 23 weeks and birthweight less than 1,000 g cared for in the delivery room in two distinct periods, when different practices were adopted immediately after birth. In the first period, 1994, all newborns (n = 56) presenting with mild respiratory discomfort were intubated soon after birth. In the second period, 1996, all patients (n = 67) received continuous pressure of 20-25 cm H<sub>2</sub>O through a nasopharyngeal tube followed by CPAP of 4-6 cm H<sub>2</sub>O to establish the functional residual capacity and prevent intubation and mechanical ventilation. None of the 123 patients received prophylactic surfactant in the delivery room. In 1994, 84% of newborns were intubated in the delivery room and 7% did not require intubation or mechanical ventilation during their hospital stay. In 1996, 40% of the newborns were intubated in the delivery room and 25% never required intubation or mechanical ventilation. In the latter group, 35% received mechanical ventilation due to respiratory distress syndrome, and the use of the new technique in the delivery room did not increase morbidity and mortality. The authors conclude that intubation in the delivery room should be performed on a case-by-case basis and used only in patients who need it. Moreover, the administration of prophylactic surfactant may change these results due to the necessity of immediate intubation.<sup>6</sup>

One of the disadvantages of intubation is the presence of a tracheal cannula which, after crossing the larynx, eliminates the intrinsic end-expiratory pressure, reducing intratracheal pressure during expiration and leading to lung collapse with consequent reduction in lung volume and in the functional residual capacity.

A study carried out in the United Kingdom followed up the changes in resuscitation maneuvers in preterm infants from 1993 to 1997. Ventilation with self-inflating bag and face mask was replaced by T-tube with a pressure-controlled face mask in 1995. With time, the frequency of tracheal intubation was cut down to half in patients with gestational age equal to or greater than 30 weeks, but remained between 80 and 85% in those with gestational age less than 30 weeks.<sup>45</sup>

Another issue related to preterm infant care that has been discussed is the transportation of the patient requiring assisted intubation and ventilation to the intensive care unit. In a recent study, 36 newborns with a mean age of 28 weeks (23-34) and birthweight of 1,180 g (480-4,200) intubated and ventilated from birth up to their transfer to the neonatal unit were submitted to continuous monitoring of the dynamic pulmonary function. They received initial pressure parameters of 18 cm H<sub>2</sub>O, PEEP of 5 cm H<sub>2</sub>O, inspiratory time of 0.3 seconds with 60 cycles/minute and FiO<sub>2</sub> for oxygen saturation between 90 and 98%. On admission to the neonatal intensive care unit, 26% had a PaCO<sub>2</sub> less than 30 mmHg, 38% had a PaO<sub>2</sub> greater than 100 mmHg, and 20% had hypocapnia with hyperoxia. The minute/kg ventilation revealed an inverse correlation with PaCO<sub>2</sub>: patients with hypocapnia had a mean of 627 ml/kg/minute and those with normocapnia had 402 ml/kg/minute. The authors concluded that the proper adjustment of minimum ventilatory parameters is quite difficult in the period between birth and transfer to the neonatal unit, and, in this case, unintentional hyperventilation is very common. Thus, special caution should be exercised to limit minute ventilation during resuscitation to prevent hypocapnia, which besides respiratory problems, may result in inappropriate cerebral autoregulation with consequent periventricular leukomalacia, hearing loss and cerebral palsy.<sup>47</sup>

In addition to the aspects mentioned above, the recommendation of tracheal intubation in a newborn in the delivery room must always take into account the resuscitator's ability and the possibility of complications that include the development of hypoxemia, apnea, bradycardia, pneumothorax, soft tissue laceration, tracheal or esophageal perforation and increase in the risk of infection.<sup>1,2</sup> A prospective study conducted at a university center used video recordings to compare the number of attempts and the time necessary to obtain a successful tracheal intubation in the delivery room in two groups: patients with gestational age less than or equal to 28 weeks and greater than 28 weeks. The procedure was successful in 54% (20/39) versus 39% (31/78) of the attempts and in 28 versus 26 seconds, with no statistical significance, and esophageal intubation was the most common cause of failure. The authors recommend that the length of 30 seconds be adjusted, since the attempts between 20 and 30 seconds were not associated with bradycardia or cyanosis.<sup>48</sup>

Currently, it has been demonstrated that preterm infants with gestational age less than 30 weeks benefit from prophylactic surfactant given in the first minutes of life through the tracheal tube,<sup>45</sup> without enough time for the correct positioning of the cannula. Thus, a recent investigation proposes suprasternal palpation, previously described in 1975,<sup>50</sup> to calculate the correct position of the tip of the tracheal cannula. This technique, applied to 54 newborns with a mean gestational age of 32 weeks (range: 24-42) and birthweight of 1,900 g (470-4.400) allowed determining the exact position of the cannula in 38 (70%) patients, compared to 54 (100%) newborns in

whom the positioning was determined via chest x-ray ( $p = 0.0001$ ). The authors state that the advantage of this technique is that it is simple, quick, noninvasive, safe and easy to perform in extremely preterm infants due to the small amount of subcutaneous tissue and cartilage, resulting in better positioning of the tracheal cannula before mechanical ventilation and in a smaller chance of intubation, especially in the right bronchus.<sup>51</sup>

Still with regard to the correct positioning of the tracheal cannula, some researchers mention that the endotracheal monitoring of expired CO<sub>2</sub> by means of color<sup>52</sup> or capnography<sup>53</sup> may be useful. In 45 patients (450-4,620 g) intubated in the delivery room and in 21 intubated in the neonatal unit, this technique helped detect 12 cases of esophageal intubation. The three false-negative results occurred in patients with severe respiratory depression.<sup>52</sup> The mean time to determine the position of the cannula was 8±3 seconds through the CO<sub>2</sub> detector, and 39±15 seconds based on clinical evaluation. Capnography also distinguished 16 cases of tracheal intubation and 11 cases of esophageal intubation,<sup>53</sup> with a mean time of 9 seconds (4-26) in capnography and 30 seconds (25-111) in clinical evaluation. Even though it is a practical procedure, precautions must be taken, since these studies only report some dozens of attempts of intubation, and some situations such as the following are not considered: inappropriate pulmonary expansion, reduced pulmonary blood flow and low tidal volumes, which may interfere with the interpretation of results.

In cases of failure of tracheal intubation or of inefficient ventilation with balloon and mask, laryngeal mask airway has been suggested. However, only newborns with gestational age greater than 34 weeks have been studied, so no experience exists with extremely preterm infants.<sup>53</sup>

The greatest concern with tracheal intubation in extremely low birthweight infants is the invasiveness of the procedure, thus requiring a highly skilled and continuously trained staff to perform it quickly and efficiently with minimal complications.<sup>11,39</sup>

### Exogenous surfactant

A meta-analysis included eight clinical trials published between 1991 and 1997 with the aim of comparing the effect of the prophylactic and therapeutic use of surfactant in respiratory distress syndrome in preterm infants with gestational age less than 30-32 weeks.<sup>49</sup> All trials were randomized and controlled using natural surfactant, which was administered via the endotracheal tube before the first respiratory movement or immediately after intubation or stabilization. The results showed reduction in the incidence of pneumothorax (6 studies with 2,515 patients; relative risk of 0.62 and 95% confidence interval of 0.42-0.89), of pulmonary interstitial emphysema (six studies with 2,037 patients; RR 0.54; 95%CI - 0.36-0.82), of bronchopulmonary dysplasia or death associated with the use of prophylactic surfactant (8 studies with 2,816 patients; RR 0.85; 95%CI - 0.76-0.95). No difference was observed as to the incidence

of necrotizing enterocolitis, patent ductus arteriosus, severe peri-intraventricular hemorrhage or retinopathy of prematurity. In newborns with less than 30 weeks, there was a reduction in the risk of neonatal death (seven studies with 1,822 patients; RR 0.62; 95%CI – 0.49-0.78) and of the risk of death or bronchopulmonary dysplasia (eight studies with 2,025 patients; RR 0.87; 95%CI – 0.77-0.97). The meta-analysis suggests that for every 100 patients who receive the prophylaxis, there is a reduction of two pneumothoraces and five deaths.

One of the main investigations<sup>55</sup> about surfactant administration in the delivery room was carried out in three U.S. maternity wards where 651 preterm infants with an estimated gestational age between 24<sup>0/7</sup> and 28<sup>6/7</sup> weeks were randomized into two groups prior to birth. The first group consisted of patients who received a bolus of 3 ml (105 mg) of natural surfactant via the endotracheal tube immediately after birth and before positive pressure ventilation. The second group was submitted to tracheal intubation within the first 9 minutes of life and to resuscitation procedures, if necessary, and at 10 minutes of life, 3 ml of surfactant was given in four doses of 0.75 ml. All patients received up to three additional doses of therapeutic surfactant when they developed respiratory distress syndrome. Survival up to hospital discharge was similar in both groups (76 *versus* 80%), as well as the need for oxygen therapy up to 36 weeks of postconceptional age (18 *versus* 13%). Since then, these authors recommend the administration of prophylactic surfactant around the 10th minute of life, after resuscitation maneuvers, in preterm infants with gestational age less than 29 weeks.

The beneficial effect of the prophylactic use of surfactant is related to the possibility of mixing it with the pulmonary fluid, reaching the alveoli before the establishment of lung injury. However, the disadvantage is that the patient has to be submitted to tracheal intubation and that there is a remarkable number of patients who do not develop respiratory distress syndrome, i.e., 35 to 55% are unnecessarily treated at a high cost.

Thus, one of the practices currently used in U.S. neonatal units consists in having a resuscitation team trained to administer prophylactic surfactant within 20-30 minutes of life to preterm infants weighing less than 1,000 g, gestational age less than 27 weeks and/or in the presence of respiratory distress.<sup>39</sup> Other units indicate the use of prophylactic surfactant in patients with less than 30 weeks of gestational age.<sup>11</sup> The teams assess the patient's stability according to four parameters: heart rate equal to or greater than 100-120 beats/minute, oxygen saturation greater than 89%, perfusion equal to or less than 3 seconds and mean arterial pressure equal to or greater than gestational age. Usually, the two first parameters are more easily verified, and the main objective is to administer surfactant as quickly as possible, before 20 minutes of life in stable patients in the delivery room.

### **Cardiopulmonary resuscitation**

Currently, cardiopulmonary resuscitation is initiated if after 30 seconds of ventilation and oxygen at 100%, the

newborn has or continues to have a heart rate less than 60 bpm. Cardiac compression is performed at the lower third of the sternum using the two-thumb method, which is the most efficient, or using two index fingers and the middle finger.<sup>56</sup> Although there are no data about the neonatal period, it is recommended that the depth of compression involve approximately one third of the anteroposterior dimension of the chest, so as to produce a palpable pulse. Ventilation and cardiopulmonary resuscitation are performed in a synchronized way, maintaining a 3:1 ratio.<sup>57</sup> Improvement is considered when the patient has a heart rate greater than 60 bpm after ventilation followed by cardiopulmonary resuscitation.<sup>1,2</sup>

The use of cardiac massage has been reported in 8% of newborns with birth weight between 401 and 1,000 g.<sup>58</sup> However, complications related to cardiopulmonary resuscitation have been reported in extremely preterm infants, such as liver laceration and rib fractures due to fragility.<sup>1,2</sup>

### **Epinephrine**

Epinephrine is indicated for heart rates less than 60 bpm after at least 30 seconds of positive pressure ventilation and oxygen at 100% followed by cardiopulmonary resuscitation.<sup>1,2</sup> Its main function seems to be related to peripheral vasoconstriction, improving oxygen supply to the heart and to the brain during cardiopulmonary resuscitation.<sup>59</sup> It is given in the dose of 0.1-0.3 ml/kg/dose of the solution at 1/10,000 (0.01-0.03 mg/kg) via endotracheal tube or intravenously. The intraosseous route is seldom used because the bones are fragile and the intraosseous space is too small, especially in preterm infants.<sup>60</sup>

The dose and route of administration of epinephrine during neonatal resuscitation have been discussed by some authors. Experiments with adult animals have shown that the beneficial effect of epinephrine is mediated by the alpha-agonist activity with vasoconstriction instead of the beta-agonist property with consequent increase in contractility and heart rate. In animal models and in adult humans, a dose of epinephrine ten times greater than the conventional recommended dose improves cerebral blood flow, left ventricular output and coronary perfusion, as well as the time of return to spontaneous circulation during ventricular fibrillation. Nevertheless, as prospective and controlled studies have not been performed, the initial dose of 1.0 mg in adults is recommended.<sup>61</sup>

There are several differences between newborns and adults as to the use of epinephrine. Firstly, 80% of newborns do not develop ventricular fibrillation as terminal cardiac activity. Newborn infants have bradycardia and high doses of epinephrine do not exert an effect on this condition. On top of that, in adults with cardiac arrest due to coronary disease, high doses of epinephrine can help myocardial perfusion, which is vital to the restoration of spontaneous circulation. However, in newborns, the terminal heart rate

results from hypoxia despite a transient increase in the heart rate and myocardial blood flow. Therefore, in this age group, the increase in coronary blood flow due to high doses of epinephrine is not critical to resuscitation success, contrary to what occurs with adults.

In newborn lambs with asphyxia-induced bradycardia, the dose of 0.05 to 0.1 mg/kg increases arterial pressure and heart rate more than the dose of 0.01 mg/kg, but it is accompanied by lower volume and cardiac output. Therefore, the dose of 0.1 mg/kg of epinephrine can be deleterious to newborns. There is a major concern with preterm infants, since they may develop peri-intraventricular hemorrhage due to hypertension that follows hypotension, especially if they receive higher doses of epinephrine than that which is currently recommended.<sup>62</sup>

Due to the lack of knowledge about the dose-response effect of epinephrine on newborns, lack of evidence that high doses are efficient during symptomatic bradycardia, lack of information about the importance of coronary pressure in newborns and in risks associated with high doses of epinephrine, a dose of 0.01 to 0.03 mg/kg in the concentration of 1:10,000 is recommended.<sup>61</sup>

With regard to the route of administration of epinephrine, the same effects are obtained with an infusion of 0.1 mg/kg via the tracheal tube and of 0.01 mg/kg intravenously, but with different cardiovascular repercussions that may have important implications for neonatal resuscitation, especially in preterm infants. The peak and length of hypertension are higher when a dose of 0.1 mg/dl is given via the tracheal tube compared to a dose of 0.01 mg/dl per intravenous infusion. As previously mentioned, the levels of arterial blood pressure in preterm infants may predispose to peri-intraventricular hemorrhage.

The fact that the lung is hypoperfused does not interfere with epinephrine absorption via the endotracheal tube, as demonstrated in lungs of newborn lambs with hypoxic pulmonary vasoconstriction and reduction in the pulmonary blood flow at 30%.<sup>61</sup>

Thus, by considering mainly the deleterious effects associated with high doses of epinephrine infused via a tracheal tube in preterm or full-term infants, it is recommendable to use the dose of 0.01 to 0.03 mg/kg or 0.1 to 0.3 ml/kg of a concentration of 1:10,000, which is the same as that given intravenously.<sup>1,2,61,63</sup>

A review has been conducted recently with the following objectives: to determine the effect of endotracheal x intravenous epinephrine, the effect of high dose *versus* a dose of 0.01 to 0.03 mg/dl and the effect of epinephrine on full-term newborns x extremely preterm bradycardic infants on mortality and morbidity. The authors did not find any randomized and controlled clinical trial and concluded that the current recommendations for its use in newborns are solely based on studies with animal models or human adults. Studies that can determine the effect of epinephrine on newborns, including extremely low birthweight ones, are necessary.<sup>64</sup>

## Volume expanders

Volume expanders may be necessary to resuscitate newborns with hypovolemia. Suspicion exists whenever there is not an appropriate response to resuscitation procedures, if there is blood loss or if there are signs of hypovolemic shock, such as pallor, poor perfusion, and weak pulses. The expander of choice is the isotonic crystalloid solution – saline solution 0.9% or Ringer's lactate solution – in the initial dose of 10 ml/kg via umbilical intravenous administration in 5 to 10 minutes.<sup>1,2</sup>

Although this practice is used, there are no investigations about the administration of crystalloids in newborns during resuscitation in the delivery room. The publication that gets closest to the near-birth period describes the treatment of 41 hypotensive newborns within the first 24 hours of life who received saline solution (n = 20) or albumin at 5% (n = 21). The goal was to maintain the mean arterial pressure at 30 mmHg in patients weighing 2,500 g or less at birth, and at 40 mmHg, for at least 30 minutes, if birthweight was greater than 2,500 g. Expansion with saline solution was as efficient as that in which albumin was used (85 *versus* 81%). Thus, the authors conclude that, due to the low cost and wide availability of saline solution, it should be the treatment of choice for treating this condition.<sup>65</sup>

Albumin should not be used due to its restricted availability, to the risk of infection and to the association with myocardial injury and an increase in neonatal mortality.<sup>66,67</sup>

## Sodium bicarbonate

Another controversial drug used for neonatal resuscitation is sodium bicarbonate, since no convincing evidence exists in favor of its use, mainly in preterm infants with gestational age less than 32 weeks.

Sodium bicarbonate is only indicated during prolonged resuscitation, when the newborn does not respond to other therapeutic measures. The dose to be infused in no less than 2 minutes is of 2 mEq/kg of the solution at 4.2% (0.5 mEq/ml).<sup>1,2</sup>

For many years acidosis was treated with bicarbonate before the administration of epinephrine, due to the reduced response to catecholamines during acidosis. However, several studies have cast some doubt on the use of bicarbonate during hypoxic lactic acidosis, since this drug may lead to a lower cardiac output, lower arterial blood pressure and lower intramyocardial pH. As the correction of acidosis depends on the elimination of CO<sub>2</sub>, if it remains in the bloodstream, it will cross the cell membranes and will increase the production of hydrogen radical, worsening intracellular acidosis and myocardial activity, even with an increase in arterial pH. Elimination of CO<sub>2</sub> depends on ventilation and pulmonary blood flow. When sodium bicarbonate is given to an inadequately ventilated patient, there will be accumulation of CO<sub>2</sub>. If cardiorespiratory arrest occurs, venous pH will increase and little blood will reach the lungs in order to eliminate the CO<sub>2</sub>. Moreover, hypercapnia prevents the gradient from cellular CO<sub>2</sub> to the



intravascular one, making CO<sub>2</sub> difficult to eliminate and worsening intracellular acidosis. Therefore, the administration of sodium bicarbonate should always be followed by efficient ventilation.<sup>61</sup>

Other possible complications of sodium bicarbonate infusion are hypernatremia and peri-intraventricular hemorrhage in preterm infants.<sup>68</sup> The undiluted sodium bicarbonate solution contains 2,000 mOsm/l, which is extremely hypertonic and independently associated with higher mortality even after a successful resuscitation. Hyperosmolarity can reduce aortic diastolic blood pressure, increase right atrial pressure and decrease lung perfusion.<sup>69</sup> Moreover, the abrupt elevation of arterial CO<sub>2</sub> pressure acts on cerebral arterioles increasing brain perfusion and consequently resulting in hemorrhage. Some authors consider that an adequate infusion of volume expanders corrects metabolic acidosis as efficiently as does bicarbonate, without the risks of sodium overload and hyperosmolarity, and suggest that sodium bicarbonate not be used for neonatal resuscitation.<sup>70</sup>

The only randomized and controlled clinical trial was conducted in India and assessed the effect of sodium bicarbonate in 55 newborns with asphyxia at birth: 28 patients (15 preterm infants) who received 4 ml/kg of sodium bicarbonate (1.8 mEq/kg) in 3-5 minutes and 27 patients (20 preterm infants) who received 4 ml/kg of dextrose at 5%. The groups were comparable as to the application of cardiopulmonary resuscitation (44 *versus* 39%), to the administration of epinephrine (37 *versus* 25%) and of volume expander (22 *versus* 11%). Despite the fact that the performed procedure did not follow the currently recommended international standards,<sup>1,2</sup> the study showed that the incidence of hypoxic-ischemic encephalopathy, brain edema and mortality were similar in both groups, thus concluding that the administration of bicarbonate did not improve the immediate neurological prognosis and survival.<sup>71</sup>

Thus, when taking into account risks and laboratory evidence of deleterious effects of sodium bicarbonate during resuscitation, one suggests that it be used only in cases of prolonged resuscitation when other measures fail. It is advisable to administer it very slowly in well-ventilated patients, who after receiving epinephrine and volume expander, have not shown an appropriate response.<sup>1,2</sup>

### **Ethical aspects**

The advancements in obstetric interventions and the introduction of new technologies that allow preterm newborns to have better survival also predispose newborns to abnormal neuropsychomotor development, which is inversely proportional to gestational age. Many of these patients who used to be regarded as hopeless have survived nowadays. This shows the necessity to have an ethical discussion about the onset of resuscitation in the delivery room, which includes moral and legal issues with great emotional and financial impact on families, health professionals and society.<sup>72</sup>

The resuscitation of an extremely low birthweight newborn proves controversial with the reduction of birthweight and gestational age, and most studies on survival contemplate only weight. Resuscitation was assessed in 118,448 patients with birthweight between 500 and 1,500 g born between 1991 and 1999 in 362 neonatal intensive care units (325 from the USA, six from Canada and 31 units from 17 other countries). Considering the range between 501 and 750 g, the survival rate that was 47% in 1991 reached 55% in 1999, whereas in the range between 751 and 1,000 g, it increased from 80% (1991) to 85% (1999).<sup>73</sup>

In 1995 and 1996, the in-hospital survival of 4,438 newborns from 14 university centers affiliated with the National Institute of Child Health and Human Development Neonatal Research Network was 11, 29, 63, 74, 86 and 89%, respectively for weight ranges of 401-500 g, 501-600 g, 601-700 g, 701-800 g, 801-900 g and 901-1.000 g.<sup>74</sup>

Also in our setting, several neonatologists have published studies carried out at public hospitals. A prospective study involving 1,416 very low birthweight infants, conducted between 1998 and 1999 by the Brazilian Neonatal Research Network, consisting of eight neonatal intensive care units of teaching hospitals located in six towns of the states of Rio de Janeiro (one unit), São Paulo (five units) and Rio Grande do Sul (two units) found in-hospital survival rates of 25 and 64%, respectively, for the groups of 500-749 g and 750-999 g.<sup>75</sup>

A cohort study including 258 extremely preterm infants with gestational age between 24 and 30 weeks born between 1998 and 2003 at a private hospital in the city of São Paulo, where all mothers have prenatal care, revealed no survival in those weighing less than 500 g, a 40% survival in 25 patients weighing between 500 and 599 g at birth, 36% in those between 600 and 699 g (n = 36), 65% in the 700-799 g group (n = 71), 77% in patients with 800-899 g (n = 66) and 75% in those between 900 and 999 g (n = 60).<sup>76</sup>

These studies show that the survival of extremely preterm infants varies with age and depends on the place of birth, and that it should be continually assessed and compared with national and international data, since these assessments help guide parents and physicians on how to manage resuscitation in the delivery room.

Although weight is an accurate measure that can be obtained immediately after birth, its reliability in predicting feasibility is limited. For instance, a preterm infant weighing 750 g can be regarded as appropriate for the gestational age of 22 to 26 weeks, but this four-week difference allows for survival rates between 0 and 66% according to U.S. data.<sup>70,77</sup> Therefore, the use of gestational age is considered a better parameter than birthweight to determine feasibility.

A review of 32 studies carried out in industrialized countries of North America, Europe and Asia with preterm babies born between 22<sup>0/7</sup> and 25<sup>6/7</sup> weeks in 1990 to 1996 showed an in-hospital survival rate of 3.4% in 1,208

patients of 22<sup>0/7</sup> to 22<sup>6/7</sup> weeks, 21% in 1,946 patients of 23<sup>0/7</sup> to 23<sup>6/7</sup> weeks, 46% in 1,623 patients of 24<sup>0/7</sup> to 24<sup>6/7</sup> weeks and 66% in 4,355 patients of 25<sup>0/7</sup> to 25<sup>6/7</sup> weeks.<sup>78</sup>

With regard to gestational age, data collected between 1998 and 2003 about infants born at a private hospital of the city of São Paulo, where all mothers have prenatal care, revealed an in-hospital survival, as follows: 23 weeks – absent, 24 weeks - 36% (12 survivors/33 live births); 25 weeks - 57% (21/37); 26 weeks - 62% (38/61); 27 weeks - 55% (17/31); 28 weeks - 76% (32/42); 29 weeks - 79% (26/33) and 30 weeks - 91% (19/21). In this study, the lengthening of pregnancy for one week, from 24 to 25 weeks, increased the chances of survival by 60%.<sup>76</sup>

In practice, unfortunately, age is not precisely known in a remarkable number of patients. In addition, neonatal clinical assessment of gestational age using the Ballard<sup>79</sup> score for the age between 22 and 28 weeks can also be inaccurate in 1.3 up to 3.3 weeks.<sup>80</sup> It should be underscored that the clinical sign of fused eyelids may be observed in approximately 20% of live births with gestational age between 24 and 27 weeks.<sup>79</sup> These facts can interfere with the decision-making process in the delivery room.

It seems advisable to recommend that resuscitation should be performed if the diagnosis of gestational age has not been previously established. The “wait and see” strategy before starting resuscitation should be eliminated, since a delay in the procedures can cause cold stress injury, hypoglycemia, hypotension and hypoxemia in newborn infants, increasing mortality and morbidity.<sup>70</sup>

In addition to survival aspects, data about development should be considered in the decision-making process including parents and physicians. Vohr et al.<sup>81</sup> assessed 1,480 extremely low birthweight infants born between 1993 and 1994 up to 18-22 months of postconceptional age. Two thirds had a rate below 85 on Bailey psychomotor developmental index and one third had a rate below 70 in the assessment of mental development, with a 49% incidence of one or more disorders (cerebral palsy, mental retardation or deafness). It is known that at the age of 5 years, the chances of extremely preterm infants having learning disabilities is threefold when compared to full-term newborns.<sup>82</sup>

Shankaran et al.<sup>83</sup> specifically evaluated 246 survivors out of 1,016 live births between 1993 and 1999 up to 18-22 months of corrected age. These patients were aged 24 weeks or less, weighed 750 g or less at birth and had a 1-minute Apgar score equal to or less than 3. Of 246 survivors, 30% had cerebral palsy, 5% presented hearing loss and 2% were blind. Bailey mental development index was below 70 in 46% of the infants and the psychomotor score was less than 70 in 36% of them. Thus, mortality and morbidity are very high in this group of patients, and this information should be shared with parents in the decision-making process, whenever possible.

Even though no common agreement exists as to “how small, small is,” several studies conducted among health professionals show they are unanimous about the unfeasibility

of resuscitation in infants with less than 23 weeks of gestational age.<sup>78</sup> The Canadian Pediatric Society and the Society of Obstetricians and Gynecologists of Canada recommend the following: not performing resuscitation in concepti with less than 23 weeks of age; deciding together with the family about the cases of 23 and 24 weeks and performing resuscitation in patients older than 25 weeks.<sup>84</sup>

Literature data confirm that resuscitation should not be indicated for patients aged less than 23 weeks or weighing less than 400 g.<sup>1,2,78</sup> After this period, if time allows so, parents should be informed about the implications of resuscitation procedures, including the possibility of sequelae from diseases associated with a specific gestational age. Moreover, the outcome of newborns in a certain neonatal unit should also be included in resuscitation decisions. Each clinical case must be analyzed separately, always trying to establish adequate communication between parents, obstetricians and pediatricians in order to decide whether resuscitation is appropriate. Most physicians agree that the delivery room is the proper place for life and death decisions.<sup>70</sup>

In our setting, no specific recommendations have been published by Bioethics Committees regarding minimum gestational age or the presence of congenital anomalies that preclude neonatal resuscitation in the delivery room. Maternity wards should collect information about the success and failure of resuscitation procedures in the delivery room, as well as data on survival, based on gestational age, birthweight and presence of congenital anomalies, so as to compare them with literature data, discuss them and define their own practices with regard to these patients.

Another ethical aspect that should be considered is the time for discontinuation of resuscitation procedures in the delivery room.

A study carried out by the Vermont Oxford Network including 196 neonatal intensive care units where 12,983 preterm infants weighing between 401 and 1,000 g born between 1994 and 1996 were assessed, revealed an 8% frequency of cardiopulmonary resuscitation in the delivery room. The comparison of 1,157 patients submitted to cardiopulmonary resuscitation or who received epinephrine with 10,826 patients who did not receive these treatments showed a survival rate of 54 and 75%, respectively. However, when patients were grouped according to their birthweight, survival without severe peri-intraventricular hemorrhage was similar (16%) in 496 preterm infants weighing between 401 and 500 g with and without cardiopulmonary resuscitation and/or epinephrine. In those weighing between 501 and 750 g, survival amounted to 37% among those who received cardiopulmonary resuscitation and/or epinephrine and to 54% in those who did not receive these treatments. In those weighing between 751 and 1,000 g, a rate of 56% was observed in those who required cardiopulmonary resuscitation and/or epinephrine and 84% in those who did not need it. Thus, most extremely preterm infants who require cardiopulmonary resuscitation and/or epinephrine at birth

survive with no evidence of severe peri-intraventricular hemorrhage. As to the prognosis of long-term outcomes, specific studies should be conducted in newborns submitted to these procedures.<sup>58</sup>

Literature data reveal that the resuscitation of a newborn after 10 minutes of asystolic cardiac arrest resulting in survival or survival without severe sequelae is quite improbable.<sup>70,85,86</sup> Resuscitation can be suspended after 15 minutes of absent heart rate despite the appropriate use of all resuscitation procedures available.<sup>1,2,87</sup>

### Final remarks

Due to controversy and lack of information about several resuscitation procedures used in extremely preterm infants, there have been a lot of animal studies and controlled randomized trials. Perhaps the next international consensus, which has been underway and whose publication is expected for December 2005, will include new practices and place emphasis on aspects related to oxygenation and ventilation of extremely low birthweight infants in the delivery room.

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