

WORKSHEET for PROPOSED Evidence-Based GUIDELINE RECOMMENDATIONS

Worksheet Author:	Home Subcommittee: PEDS/NRP
Author's Home Resuscitation Council: AHA	Date Submitted to Subcommittee: <u>11/14/2003; 15Aug04;</u> <u>14Jan05; 26Jan05</u>

STEP 1: STATE THE PROPOSAL. State if this is a proposed new guideline; revision to current guideline; or deletion of current guideline.

Existing guideline, practice or training activity:

Revision to current guideline:

Neonatal Resuscitation Textbook, AHA/AAP, 2000, page 3-24 - 3-26: "A noticeable rise and fall of the chest is by far the best indication that the mask is sealed and the lungs are being inflated. The newborn should appear to be taking a normal or "easy" breath. ... In order to establish a gaseous volume (functional residual capacity) in the newly born baby, the first few breaths will often require higher pressures and longer inflation times than will subsequent breaths. This requirement for increased and more prolonged pressure is more likely to be found in a baby who is not breathing spontaneously. ... Although you should ventilate with the lowest pressure required to move the chest adequately, initial breaths may require pressures of more than 30cm H₂O. Subsequent breaths usually require less pressure. ... Premature babies have even smaller breath sizes, with some as small as 5 to 10mL. However, they may also have stiffer lungs, thus requiring higher inflation pressures to deliver these smaller volumes. ... During the initial stages of neonatal resuscitation, breaths should be delivered at a rate of 40 to 60 breaths per minute..."

Pediatrics 2000; 106(3). URL: <http://www.pediatrics.org/cgi/content/full/3/e29>; *neonatal resuscitation*, pages 8-9: "Although the pressure required for establishment of air breathing is variable and unpredictable, higher inflation pressures (30-40 cm H₂O or higher) and longer inflation times may be required for the first several breaths than for subsequent breaths. Visible chest expansion is a more reliable sign of appropriate inflation pressures than any specific manometer reading. The assisted ventilation rate should be 40 to 60 breaths per minute (30 breaths per minute when chest compressions are also being delivered)."

Step 1A: Refine the question; state the question as a positive (or negative) hypothesis. State proposed guideline recommendation as a specific, positive hypothesis. Use single sentence if possible. Include type of patients; setting (in-/out-of-hospital); specific interventions (dose, route); specific outcomes (ROSC vs. hospital discharge).

Limited data from animal studies and clinical trials exist regarding initial ventilation of the asphyxiated newly born infant. Several alternative hypotheses may be generated:

- H1. Positive pressure ventilation alone is effective in the resuscitation of asphyxiated newly born infants.
- H2. Observing an increase in heart rate within 30 seconds is the primary measure of adequate initial ventilation.
- H3. Observing chest wall movement assesses the adequacy of initial ventilation; pressures in excess of 30 cm H₂O may be required.
- H4. Prolonged, or sustained inflations (> 1 second) are needed for the initial inflation of asphyxiated, term infants.
- H5. Optimal artificial ventilation is delivered at a rate of 30 - 40 breaths per minute.

Step 1B: Gather the Evidence; define your search strategy. Describe search results; describe best sources for evidence.

Initial search was through Medline for articles from 1966 - present, followed by hand searching review articles and by examining the citations of individual articles (especially for references prior to 1966). An additional strategy was to search for articles that have referenced a specific article, e.g. search for all articles that have referenced Vyas, H, et al. *J Pediatr* 99: 635-639, 1981. Searched using following terms: Infant, Newborn; Infant, Premature; resuscitation or cardiopulmonary resuscitation or respiration, artificial; positive-pressure respiration; asphyxia neonatorum.

List electronic databases searched (at least MEDLINE (<http://igm.nlm.nih.gov/>) and hand searches of journals, review articles, and

books.

Medline, Review articles (see Citation List)

- State major criteria you used to limit your search; state inclusion or exclusion criteria (e.g., only human studies with control group? no animal studies? N subjects > minimal number? type of methodology? peer-reviewed manuscripts only? no abstract-only studies?)

No abstract only studies were included. Only peer-reviewed studies were included. Excluded studies from stillborn infants and isolated lung preparations. • Number of articles/sources meeting criteria for further review: Create a citation marker for each study (use the author initials and date or Arabic numeral, e.g., "Cummins-1"). If possible, please supply file of best references; End Note 4+ preferred as reference manager, though other reference databases acceptable.

From the above strategy 728 articles were identified; 20 are included for review based on exclusion criteria.

STEP 2: ASSESS THE QUALITY OF EACH STUDY

Step 2A: Determine the Level of Evidence. For each article/source from step 1, assign a level of evidence—based on study design and methodology.

Level of Evidence	Definitions (See manuscript for full details)
Level 1	Randomized clinical trials or meta-analyses of multiple clinical trials with substantial treatment effects
Level 2	Randomized clinical trials with smaller or less significant treatment effects
Level 3	<u>Prospective</u> , controlled, non-randomized, cohort studies
Level 4	<u>Historic</u> , non-randomized, cohort or case-control studies
Level 5	<u>Case series</u> ; patients compiled in serial fashion, lacking a control group
Level 6	Animal studies or mechanical model studies
Level 7	Extrapolations from existing data collected for other purposes, theoretical analyses
Level 8	Rational conjecture (common sense); common practices accepted before evidence-based guidelines

Step 2B: Critically assess each article/source in terms of research design and methods.

Was the study well executed? Suggested criteria appear in the table below. Assess design and methods and provide an overall rating. Ratings apply within each Level; a Level 1 study can be excellent or poor as a clinical trial, just as a Level 6 study could be excellent or poor as an animal study. Where applicable, please use a superscripted code (shown below) to categorize the primary endpoint of each study. For more detailed explanations please see attached assessment form.

Component of Study and Rating	Excellent	Good	Fair	Poor	Unsatisfactory
Design & Methods	Highly appropriate sample or model, randomized, proper controls AND Outstanding accuracy, precision, and data	Highly appropriate sample or model, randomized, proper controls OR Outstanding accuracy, precision, and data	Adequate, design, but possibly biased OR Adequate under the circumstances	Small or clearly biased population or model Weakly defensible in its class, limited data or measures	Anecdotal, no controls, off target end-points Not defensible in its class, insufficient data or measures

	collection in its class	collection in its class			
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A = Return of spontaneous circulation C = Survival to hospital discharge E = Other endpoint

B = Survival of event D = Intact neurological survival

Step 2C: Determine the direction of the results and the statistics: supportive? neutral? opposed?

DIRECTION of study by results & statistics:	SUPPORT the proposal	NEUTRAL	OPPOSE the proposal
Results	Outcome of proposed guideline superior, to a clinically important degree, to current approaches	Outcome of proposed guideline no different from current approach	Outcome of proposed guideline inferior to current approach

Step 2D: Cross-tabulate assessed studies by a) level, b) quality and c) direction (i.e., supporting or neutral/ opposing); **combine and summarize.** Exclude the *Poor* and *Unsatisfactory* studies. Sort the *Excellent*, *Good*, and *Fair* quality studies by both *Level and Quality of evidence*, and *Direction of support* in the summary grids below. Use citation marker (e.g. author/ date/source). In the *Neutral* or *Opposing* grid use bold font for *Opposing* studies to distinguish them from merely neutral studies. Where applicable, please use a superscripted code (shown below) to categorize the primary endpoint of each study.

Supporting Evidence

- H1. Positive pressure ventilation alone is effective in the resuscitation of asphyxiated newly born infants.
- H2. Observing an increase in heart rate within 30 seconds is the primary measure of adequate initial ventilation.
- H3. Observing chest wall movement assesses the adequacy of initial ventilation; pressures in excess of 30 cm H2O may be required.
- H4. Prolonged, or sustained inflations (> 1 second) are needed for the initial inflation of asphyxiated, term infants.
- H5. Optimal artificial ventilation is delivered at a rate of 30 - 40 breaths per minute.

Quality of Evidence	Excellent									
	Good						Vyas 1981b(H3) ^E Boon 1979a(H3, H4, H5) ^E Boon 1979b(H3, H4, H5) ^E			
	Fair				Milner 1984(H3, H4) ^E Hoskyns 1987(H3) ^E	Karlberg 1962(H3) ^E				
		1	2	3	4	5	6	7	8	
		Level of Evidence								

A = Return of spontaneous circulation C = Survival to hospital discharge E = Other endpoint – inflation pressure
 B = Survival of event D = Intact neurological survival F = Other endpoint – inspiratory time

STEP 3. DETERMINE THE CLASS OF RECOMMENDATION. Select from these summary definitions.

CLASS	CLINICAL DEFINITION	REQUIRED LEVEL OF EVIDENCE
Class I <i>Definitely recommended.</i> Definitive,	excellent evidence provides support. • Always acceptable, safe • Definitely useful • Proven in both efficacy & effectiveness	• Must be used in the intended manner for proper clinical indications. • One or more Level 1 studies are present (with rare exceptions) • Study results consistently positive and compelling
Class II:	<i>Acceptable and useful</i> • Safe, acceptable • Clinically useful	• Not yet confirmed definitively • Most evidence is positive • Level 1 studies are absent, or inconsistent, or lack power
• <i>Class IIa: Acceptable and useful</i>	Good evidence provides support • Safe, acceptable • Clinically useful	• Considered treatments of choice • Generally higher levels of evidence

<ul style="list-style-type: none"> • Class IIb: <i>Acceptable and useful</i> 	Fair evidence provides support <ul style="list-style-type: none"> • Safe, acceptable • Clinically useful • Considered optional or alternative 	treatments <ul style="list-style-type: none"> • Generally lower or intermediate levels of evidence • Generally, but not consistently, positive results
Class III: <i>Not acceptable, not useful, may be</i>	<i>harmful</i> <ul style="list-style-type: none"> • Unacceptable • Not useful clinically 	<ul style="list-style-type: none"> • May be harmful. • No positive high level data
	Indeterminate <ul style="list-style-type: none"> • Research just getting started • Continuing area of research • No recommendations until 	further research <ul style="list-style-type: none"> • Minimal evidence is available • Higher studies in progress • Results inconsistent, contradictory

- No evidence of harm
- Results are consistently positive

- Some studies suggest or confirm harm.
- Results not compelling

STEP 3: DETERMINE THE CLASS OF RECOMMENDATION. State a **Class of Recommendation** for the Guideline Proposal. State either **a) the intervention**, and then the conditions under which the intervention is either Class I, Class IIA, IIB, etc.; or **b) the condition**, and then whether the intervention is Class I, Class IIA, IIB, etc.

Intervention: Establishing effective ventilation should be the primary objective in the management of the apneic and/or bradycardic newly born infant in the delivery room (LOE 5, 6).

Final Class of recommendation: Class I - Definitely recommended

Intervention: In the bradycardic infant, a prompt improvement in heart rate is the primary measure of adequate initial ventilation; chest wall movement should be assessed if heart rate does not improve (LOE 5, 6).

Final Class of recommendation: Class IIA-Acceptable & useful; good evidence

Intervention: Initial peak inflating pressures needed are variable and unpredictable and should be individualized to achieve an increase in heart rate and/or movement of the chest with each breath: Where pressure is being monitored, an initial inflation pressure of 20 cm H₂O may be effective, but 30-40 cm H₂O or higher may be required in some term babies (LOE 5).

If pressure is not being monitored, the minimal inflation required to achieve an increase in heart rate should be used.

There is insufficient evidence to recommend an optimum inflation time

Final Class of recommendation: Class IIB-Acceptable & useful; fair evidence

Intervention: Artificial ventilation should be delivered at a rate of 30 to 60 breaths per minute to promptly achieve or maintain a heart rate of greater than 100 beats per minute (LOE 8).

Final Class of recommendation: Indeterminate-minimal evidence or inconsistent

REVIEWER'S PERSPECTIVE AND POTENTIAL CONFLICTS OF INTEREST: Briefly summarize your professional background, clinical specialty, research training, AHA experience, or other relevant personal background that define your perspective on the guideline proposal. List any potential conflicts of interest involving consulting, compensation, or equity positions related to drugs, devices, or entities impacted by the guideline proposal. Disclose any research funding from involved companies or interest groups. State any relevant philosophical, religious, or cultural beliefs or longstanding disagreements with an individual.

Associate Professor of Pediatrics at Indiana University School of Medicine; Certified by the American Board of Pediatrics Sub-Board of Neonatal-Perinatal Medicine; Co-chair of the American Academy of Pediatrics Neonatal Resuscitation Program Steering Committee.

I have no conflict of interest

REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK: Summarize your final evidence integration and the rationale for the class of recommendation. Describe any mismatches between the evidence and your final Class of Recommendation. "Mismatches" refer to selection of a class of recommendation that is heavily influenced by other factors than just the evidence. For example, the evidence is strong, but implementation is difficult or expensive; evidence weak, but future definitive evidence is unlikely to be obtained. Comment on contribution of animal or mechanical model studies to your final recommendation. Are results within animal studies homogeneous? Are animal results consistent with results from human studies? What is the frequency of adverse events? What is the possibility of harm? Describe any value or utility judgments you may have made, separate from the evidence. For example, you believe evidence-supported interventions should be limited to in-hospital use because you think proper use is too difficult for pre-hospital providers.

The issue of providing initial ventilation in the delivery room can be divided into 2 basic components:

1. The device, or mechanism of delivering positive pressure ventilation (PPV; self-inflating vs flow-inflating vs t-piece)

2. The application of ventilation.

Examination of the various devices currently available for use in the delivery room is being considered in a separate worksheet.

The application of ventilation may be further divided into its various components: Peak inflating pressure (as a surrogate for tidal volume), inflation time, and rate. CPAP/PEEP is being addressed in a separate worksheet, but ultimately must also be incorporated into the present discussion. These components of ventilation must then be further evaluated with respect to the initial breaths vs subsequent breaths. Differences between term and preterm babies must also be considered, as well as differences between apneic/asphyxiated infants with "normal" lungs and those with pathology (pneumonia, hyaline membrane disease, meconium aspiration, etc.). The adequacy of lung inflation has also proven to be difficult to determine in an objective manner. Current recommendations focus on peak inflating pressures or observations of chest rise/chest wall movement. Measurement of tidal volume may provide the best assessment of lung inflation. There is a lack of clinical studies that evaluate the best approach to apply artificial ventilation to depressed newborn babies. The current recommendations are based on animal studies or clinical studies with weak evidence that measured mainly pulmonary function in the delivery room during resuscitation. The focus of the present worksheet is on initial ventilation of term infants in the delivery room; preterm babies are being considered in a separate worksheet.

The effectiveness of positive pressure ventilation in the resuscitation of asphyxiated newborn infants has been established through a series of animal experiments (Adams 1964, Campbell 1966, Cross 1964, Cross 1966, Dawes 1963, Godfrey 1968). These meticulous studies provide detailed descriptions of the cardiorespiratory and metabolic responses to severe asphyxia in newborn mammals of several species. The qualitative changes in the pattern of respiratory activity, heart rate and blood pressure are similar among species. These studies demonstrate that positive pressure ventilation alone is effective for resuscitation of newborn animals in secondary apnea provided that mean arterial blood pressure is above a critical value. The first sign of successful resuscitation is an increase in heart rate. The effectiveness of positive-pressure ventilation as well as the prompt increase in heart rate in response to positive pressure ventilation has also been demonstrated in human case series (Ditchburn 1966, Palme-Kilander 1993).

Several small series have examined the pressure and volume changes in the healthy, term newborn with the onset of spontaneous respiration (Karlberg 1962, Mortola 1982, Vyas 1981b, Vyas 1986). Peak inspiratory pressures generated were highly variable. In the study by Vyas, et al. (Vyas 1986), mean inspiratory pressure, measured in the lower esophagus, was -52 cm H₂O (range -28 to -105). The phenomenon of an "opening pressure" observed in earlier studies was rarely demonstrated in later studies.

Inspiratory volumes of ~35 to 45ml were similar among studies. A functional residual capacity (FRC) could be demonstrated by the end of the first breath and correlated with the inspiratory volume, and possibly was related to inspiratory time.

There are no randomized studies comparing different strategies of artificial ventilation for depressed term newborn babies. Several case series have examined the physiologic responses of asphyxiated term and preterm infants to resuscitation (Boon 1979a, Boon 1979b, Hoskyns 1987, Hull 1969, Milner 1984, Palme-Kilander 1993, Upton 1991). These studies included a limited number of babies (9 to 42), the vast majority of whom were born by cesarean section. As with spontaneously breathing infants, initial inspiratory pressures were highly variable, ranging between 18 to 60cm H₂O (mean 30 to 40cm H₂O), in order to deliver an adequate tidal volume. Chest movement as an indicator of adequate ventilation was mentioned in one study (Upton 1991). In one study (Palme-Kilander 1993), two thirds of the infants studied required peak inflation pressures exceeding 50cm H₂O to achieve adequate minute ventilation. In this study ventilation was found to be “satisfactory” if the heart rate increased to greater than 130 beats/minute within 5-15 seconds. With subsequent breaths peak inspiratory pressures were found to be somewhat less, mean 20-29cm H₂O (range 14-42 cm H₂O). In these studies inspiratory time was uncontrolled and varied from 0.5 to 2 seconds. A prolonged inflation time of 5 seconds was used for the first breath in a series of 9 patients (Vyas 1981a). Peak inspiratory pressure was maintained at 30cm H₂O either by square wave (n=4) or by a slow rise in pressure (n=5). Both maneuvers produced a 2-fold increase in FRC compared with historic controls. Where noted, inflation rates were maintained at 30 to 40 breaths/minute.

Based on the limited available data, the following statements are made concerning initial ventilation of the apneic, bradycardic newly born infant in the delivery room:

1. When properly performed, positive pressure ventilation alone is effective in resuscitation of most apneic and/or bradycardic newly born infants (LOE 5, 6) (Adamsons 1964, Campbell 1966, Dawes 1963, Godfrey 1968, Ditchburn 1966, Palme-Kilander 1993, Perlman 1995).
2. The primary measure of adequate initial ventilation is prompt improvement in heart rate (LOE 5, 6) (Adamsons 1964, Campbell 1966, Dawes 1963, Godfrey 1968, Palme-Kilander 1993); chest wall movement has been described but not adequately assessed (LOE 5, 6) (Upton 1991, Campbell 1966).
3. In term infants, initial inflations, either spontaneous or assisted, serve to initiate a functional residual capacity (LOE 5) (Karlberg 1962, Mortola 1982, Vyas 1981b, Vyas 1986, Boon 1979b, Hull 1969, Upton 1991, Vyas 1981a). The optimum pressure, inflation time and flow rate required have not been determined.
4. In case series examining the physiologic changes with initial ventilation of human neonates, the peak pressures used to initiate ventilation were variable (18-60 cm H₂O); flow rates and inspiratory times were seldom reported. Average initial peak inflating pressures of 30 to 40 cm H₂O (inflation time undefined) were used to successfully ventilate unresponsive term infants (LOE 5) (Boon 1979a, Boon 1979b, Hull 1969, Milner 1984, Palme-Kilander 1993, Upton 1991, Vyas 1981a). In a single small series, a sustained inflation pressure at 30 cm H₂O for 5 seconds for the first breath was found to be effective in establishing lung volume in term infants requiring resuscitation; the risk and benefits of this practice have not been evaluated. (LOE 5) (Vyas 1981a)
5. Artificial ventilation rates of 30 to 60 breaths per minute are commonly used, but have not been investigated (LOE 8).

Preliminary draft/outline/bullet points of Guidelines revision: Include points you think are important for inclusion by the person assigned to write this section. Use extra pages if necessary.

Citation List

	Citation Marker

<p>Adamsons 1964</p>	<p>Adamsons, K., Jr., R. Behrman, et al. (1964). "Resuscitation by positive pressure ventilation and Tris-hydroxymethylaminomethane of rhesus monkeys asphyxiated at birth." <i>J Pediatr</i> 65: 807-18.</p> <p>Rhesus monkeys delivered by cesarean section were asphyxiated under controlled environmental conditions and then resuscitated by positive pressure ventilation with oxygen. In one half of the monkeys an infusion of Tris and glucose was given into the umbilical vein during resuscitation to restore the arterial pH rapidly to normal values. This reduced the time required to establish spontaneous breathing and increased the initial oxygen uptake. There was a linear relationship between duration of asphyxia and the return of respiratory function: for each minute after the last gasp that resuscitation was deferred, subsequent onset of gasping was delayed about 2 minutes and spontaneous breathing about 4 minutes. Nearly one half of the asphyxiated animals developed respiratory difficulties similar to those seen in human infants suffering from the respiratory distress syndrome.</p> <p>Comment:</p> <p>Fetal rhesus monkeys were delivered by cesarean section and were asphyxiated under controlled environmental conditions. Heart rate and blood pressure increased within 30 seconds of initiating positive pressure ventilation in 6 of 12 animals in secondary apnea, following 10 minutes of asphyxia. In the remaining 6 animals, closed cardiac massage was applied and caused a "prompt response." Mean arterial blood pressure was significantly lower in animals requiring cardiac massage compared with those that responded to positive pressure ventilation alone. Pressures of 30-40 cm H₂O were used during initial lung expansion and 10-30 cm H₂O for subsequent breaths.</p>
<p>Boon 1979a</p>	<p><i>LOE 6; supports H1, H2 and H3</i></p> <p>Boon, A. W., A. D. Milner, et al. (1979). "Physiological responses of the newborn infant to resuscitation." <i>Arch Dis Child</i> 54(7): 492-8.</p> <p>Lung ventilation, endotracheal, and intraoesophageal pressures were measured during standard resuscitation of 20 asphyxiated babies born by caesarean section. The most common response to resuscitation was the production of a large positive intraoesophageal pressure. An opening pressure greater than 2.0 kPa was required to expand the lungs of most of these babies. The need for resuscitation was associated with prolonged maternal anaesthesia before delivery.</p> <p>Comment:</p> <p>Pulmonary mechanics were examined in 19 term (1 preterm) asphyxiated infants delivered by cesarean section. A modified T-piece was used with a spring-loaded valve set at 30 cm H₂O. Asphyxia was indicated by apnea with a falling heart rate, hypotonia with no response to suctioning, and cyanosis or pallor (Apgar score of 3 or less). Breaths were delivered at a rate of 30-40 per minute with an inflation time of approximately 1 second.</p>
<p>Boon 1979b</p>	<p><i>LOE 5; neutral H3, H4 and H5</i></p> <p>Boon, A. W., A. D. Milner, et al. (1979). "Lung expansion, tidal exchange, and formation of the functional residual capacity during resuscitation of asphyxiated neonates." <i>J Pediatr</i> 95(6): 1031-6.</p> <p>Ventilatory exchange and endotracheal and esophageal pressures were</p>

<p>Campbell 1966</p>	<p>measured during resuscitation of asphyxiated neonates born by cesarean section. In contrast to spontaneously breathing, vaginally born babies, an opening pressure had to be exceeded before lung expansion occurred. Subsequently there was usually a gradual increase in gaseous exchange over the first few lung inflations. A further rise in lung compliance occurred with the baby's inspiratory efforts. The functional residual capacity was formed with or without active inspiratory efforts by the baby, although gaseous retention occurred more rapidly as a result of the infant's inspiration.</p> <p>Comment: Pulmonary mechanics were examined in 19 term (1 preterm) asphyxiated infants delivered by cesarean section. (<i>Same infants as in Boon 1979a.</i>) A modified T-piece was used with a spring-loaded valve set at 30 cm H₂O. Asphyxia was indicated by apnea with a heart rate below 100 bpm, hypotonia with no response to suctioning, and cyanosis or pallor (Apgar score of 3 or less). The babies' lungs were inflated at a rate of 30-40 bpm using an inflation time of approximately 1 second. Tidal volume increased from a mean of 18.6 ml with the first inflation to 28.5 ml at 30 seconds.</p> <p><i>LOE 5; neutral H3, H4 and H5</i></p>
<p>Cross 1964</p>	<p>Campbell, A. G. M., K. W. Cross, et al. (1966). "A comparison of air and O₂ in a hyperbaric chamber or by positive pressure ventilation, in the resuscitation of newborn rabbits." <i>J Pediatr</i> 68(2): 153-63. Controlled trials were made of different methods of resuscitation in young rabbits, subjected to asphyxia or anoxia to beyond the last gasp. Hyperbaric O₂ was significantly less effective than positive pressure ventilation with O₂. Positive pressure ventilation with air was as effective as with O₂.</p> <p>Comment: Fetal and newborn rabbits were asphyxiated under controlled environmental conditions to compare the effectiveness of resuscitation with hyperbaric oxygen with resuscitation using positive pressure ventilation. Cardiac massage was performed when heart rate stopped or the heart rate did not increase within 30 seconds of initiating positive pressure ventilation. Study provides a detailed description of the sequence of cardiopulmonary events during asphyxia of the newborn rabbit. Demonstrates that positive pressure ventilation alone is effective for resuscitation from asphyxia following last spontaneous gasp. Approximately 85% of fetal and newborn rabbits, resuscitated an average of 4 minutes following the last spontaneous gasp, recovered with positive pressure ventilation alone or PPV plus cardiac massage. The first sign of successful resuscitation was an increase in heart rate. NB: Lung inflation was determined by observing chest wall movements.</p> <p><i>LOE 6; supports H1 and H2</i></p>
<p>Cross 1966</p>	<p>Cross, K. W., G. S. Dawes, et al. (1964). "Hyperbaric oxygen and intermittent positive-pressure ventilation in resuscitation of asphyxiated newborn rabbits." <i>Lancet</i> 2: 560-2.</p> <p>Comment:</p>

	<p>Preliminary report of data presented in Campbell 1966.</p> <p><i>LOE 6; supports H1 and H2</i></p> <p>Cross, K.W. (1966). "Resuscitation of the asphyxiated infant." <u>Br Med Bull</u> 22(1): 73-8.</p> <p>Comment: This is a review article, but is included in this section as it demonstrates the qualitative physiologic similarities in the response to asphyxia among newborn mammals of different species (rabbit, monkey, and lamb). With the onset of asphyxia there is a characteristic cycle of events. Primary apnea is followed by a variable period of gasping after which the animal goes into secondary apnea. In all species studied, respiratory activity ceases before effective cardiac activity fails. "This is in contrast to the adult, in which acute asphyxia usually causes abrupt circulatory failure before respiratory efforts cease." Heart rate decreases immediately while blood pressure tends to increase initially and then falls. In all species "ventilation of the lungs...effects a rapid and complete restoration of the cardiovascular condition to normal." An increase in heart rate is the first sign of recovery in response to positive pressure ventilation. Cardiac massage is required when the mean arterial blood pressure falls below a critical level.</p> <p><i>LOE6; supports H1 and H2</i></p>
<p>Dawes 1963</p>	<p>Dawes, G. S., H. N. Jacobson, et al. (1963). "The treatment of asphyxiated, mature foetal lambs and rhesus monkeys with intravenous glucose and sodium carbonate." <u>J Physiol</u> 169: 167-84.</p> <p>Comment: Controlled experiments in near-term fetal lambs and rhesus monkeys. Description of metabolic and cardiopulmonary responses to asphyxia. Artificial ventilation alone was effective in resuscitating the majority of animals following last spontaneous gasp, provided that the mean arterial blood pressure was greater than 15 mmHg.</p> <p><i>LOE 6; supports H1 and H2</i></p>
<p>Ditchburn 1966</p>	<p>Ditchburn, R. K., Hull, D. and Segall, M. M. (1966). "Oxygen uptake during and after positive-pressure ventilation for the resuscitation of asphyxiated newborn infants." <u>Lancet</u> 2: 1096-99.</p> <p>Comment: Case series of 31 full term infants delivered by cesarean section who received tracheal intubation and positive-pressure ventilation "(1) immediately after delivery of the infant if apnea was accompanied by bradycardia, hypotonia and cyanosis or pallor, or (2) within 4 minutes of delivery if the infant did not commence breathing and its clinical state was deteriorating despite simple resuscitative measures. A slow or falling heart rate was usually considered a strong indication for positive pressure ventilation." Positive-pressure ventilation was administered at a rate of 30-40 breaths per minute, 20-30 ml per breath, with peak inflating pressures of 18-25 mmHg (~24-34 cm H₂O), and 30-60% oxygen. Mean rates of oxygen uptake (5.6-6.5 ml/kg/min) were similar to the rates of oxygen consumption observed in somewhat older infants of similar weight. Based</p>

<p>Milner 1984</p>	<p>healthy infants on the day of birth.</p> <p>Comment: Case series of asphyxiated term infants, primarily delivered by cesarean section, resuscitated by positive pressure ventilation. Apparatus set to deliver a "stroke volume" of 40 ml yielded initial inflation pressures of 18 to 48 cm H₂O (mean 27); subsequent pressures ranged from 14 to 35 cm H₂O. FRC established in the first minute of positive pressure ventilation.</p> <p><i>LOE 5; supports H3</i></p> <p>Karlberg, P. and G. Koch (1962). "Respiratory studies in newborn infants. III. Development of mechanics of breathing during the first week of life. A longitudinal study." <u>Acta Paediatr</u> (Suppl 135): 121-9.</p>
<p>Mortola 1982</p>	<p>Comment: Case series examining pulmonary mechanics with the onset of spontaneous respiration primarily in full term infants. Pressure/volume changes recorded with first breaths demonstrated an initial tidal volume of 12-67 ml; with negative intraesophageal pressures of up to 70 cm H₂O (range -10 to -70). In one group of babies it was noted that "inflation of any significant volume took place only after a negative intrathoracic pressure of 20-40 cm H₂O was created."</p> <p><i>LOE 5; neutral H3</i></p> <p>Milner, A. D., H. Vyas, et al. (1984). "Efficacy of facemask resuscitation at birth." <u>Br Med J (Clin Res Ed)</u> 289(6458): 1563-5. The efficacy of facemask resuscitation was assessed by measuring the expiratory tidal volume during the first three inflations in nine babies with birth asphyxia and comparing the results with those obtained in a further nine babies resuscitated after endotracheal intubation. The facemask system was relatively inefficient, with tidal exchange less than one third of that seen after intubation and rarely sufficient to produce adequate alveolar ventilation. Successful resuscitation depended on stimulating the baby to make his own respiratory efforts.</p>
<p>Palme-Kilander 1993</p>	<p>Comment: Case controlled study comparing facemask resuscitation with endotracheal intubation. Peak inflation pressures similar between the two groups (range 24-36 cm H₂O). The inefficiency of facemask ventilation was attributed to relatively short inspiratory time.</p> <p><i>LOE 4; neutral H3 and H4</i></p> <p>Mortola, J. P., J. T. Fisher, et al. (1982). "Onset of respiration in infants delivered by cesarean section." <u>J Appl Physiol</u> 52(3): 716-24. We studied the ventilatory parameters and the pattern of breathing including the onset of respiration in 20 healthy infants immediately after cesarean-section delivery. In eight of the infants further measurements were obtained at 60 min of life. The pattern of breathing immediately after delivery is very irregular with a marked tendency to keep the lung inflated mainly through interruptions of expiration. After the first expiration some air remains in the lung representing the formation of functional residual capacity (FRC). FRC obtained with the first breath is proportional to the previous inspired volume and is the largest contribution towards the full</p>

<p>Perlman 1995</p>	<p>establishment of FRC. Tidal volume and FRC of the first breath are similar to that reported in babies delivered vaginally, which suggests that the forces required for lung inflation are similar in the two groups of infants. The first breath tends to be deeper and slower and has a longer expiratory time than subsequent breaths. At 60 min of life the respiratory pattern becomes more regular, tidal volume is further decreased, and respiratory frequency is increased through a reduction of expiratory time.</p> <p>Comment: Case series examining pulmonary mechanics with the onset of spontaneous respiration in full term infants delivered by cesarean section. First breaths characterized by marked variability of frequency and tidal volume. FRC is correlated to the first inspiratory volume. The first breath is deeper and slower primarily due to a long expiratory time.</p> <p><i>LOE 5; supports H3 and H4</i></p> <p>Palme-Kilander, C. and R. Tunell (1993). "Pulmonary gas exchange during facemask ventilation immediately after birth." <u>Arch Dis Child</u> 68(1 Spec No): 11-6.</p> <p>The rate of carbon dioxide production (VCO₂), heart rate, and oxygen saturation were recorded during resuscitation in 30 newborn infants. Twenty eight infants were ventilated through a facemask only and two were intubated after initial facemask ventilation. Five neonates were born at full term, eight had a gestational age of 32-36 weeks, and 17 of 27-31 weeks. Towards the end of the five minute study period, the VCO₂ in ventilated infants, born after 32 weeks or more, was not different from that of spontaneously breathing infants. Neonates with a gestational age of 27-31 weeks showed a low VCO₂, particularly when no reflex response from the baby was recorded, with a significant increase if a reflex response was elicited. Ventilation was found to be satisfactory if the heart rate increased to 130 beats/min or more within 5-15 seconds or if the oxygen saturation, measured in the right hand, was 70% or more.</p> <p>Comment: Case series including term and preterm infants. Inspiratory time 0.5 –2.0 seconds; Mean inflation pressures 25-85 cm H₂O.</p> <p><i>LOE 5; supports H2; neutral H3, H4 and H5</i></p>
<p>Upton 1991</p>	<p>Perlman, J. M. and R. Risser (1995). "Cardiopulmonary resuscitation in the delivery room. Associated clinical events." <u>Arch Pediatr Adolesc Med</u> 149(1): 20-25.</p> <p>OBJECTIVES: To determine (1) what percentage of infants require chest compressions and medications as part of resuscitation in the delivery room, (2) the associated clinical events contributing to neonatal depression, and (3) the neonatal outcome of such children. DESIGN: Observational study. SETTING: Urban county hospital. RESULTS: For 2 years, 39 (0.12%) of 30,839 infants were administered chest compressions and/or epinephrine as part of cardiopulmonary resuscitation in the delivery room. Fifteen were term infants and 24 were premature. Five term infants had evidence of severe fetal acidemia (FA) (umbilical cord arterial pH <7.00 and/or base deficit > or = -14 mEq/L); two died secondary to severe brain injury, and the neurologic examinations showed abnormalities in the three survivors. The 10 infants without severe FA exhibited an uncomplicated neonatal course. Five infants had evidence of severe FA;</p>

	<p>the neurologic examination showed abnormalities in four. Of the remaining 19 infants without severe FA, four died and five additional infants have moderate to severe brain injury. Abnormal outcome was more likely to occur with severe FA ($P < 0.002$). The presumed clinical events contributing to the neonatal depression were severe FA ($n = 10$), malpositioning of the endotracheal tube ($n = 5$), and ineffective or improper initial ventilatory support ($n = 24$). CONCLUSIONS: Cardiopulmonary resuscitation in the delivery room, resulting in administration of chest compressions and medications, is a rare event. Approximately one third of the infants had evidence of severe FA; in the remaining two thirds, ineffective or improper initial ventilatory support was the presumed mechanism for the continued neonatal depression. The appropriate therapeutic response to continuing neonatal depression should be to optimize ventilatory support before administering chest compressions or medications.</p>
Vyas 1981a	<p>Comment: Confirms primary importance of proper, effective initial ventilatory support in resuscitation of asphyxiated newborns in the delivery room.</p> <p><i>LOE 5; supports H1</i></p> <p>Upton, C. J. and A. D. Milner (1991). "Endotracheal resuscitation of neonates using a rebreathing bag." <i>Arch Dis Child</i> 66(1 Spec No): 39-42. Thirty asphyxiated neonates were resuscitated endotracheally with an anaesthetic rebreathing bag. The system was not limited either by pressure or by volume and chest movement was used as the criterion for adequate inflation. Inflation pressure and flow were recorded during resuscitation, and flow was integrated to obtain volume. Median mean pressure over the first 10 inflations was 40 cm H₂O and this dropped during later resuscitation to 29 cm H₂O. The volume delivered did not change significantly, so volume divided by pressure increased from a median of 0.18 to 0.35 ml/kg/cm H₂O. Fourteen infants formed part of their functional residual capacity with artificial ventilation and five with spontaneous breaths. Eleven infants showed no evidence of functional residual capacity formation. In the 22 preterm infants there was a strong association between absence of functional residual capacity formation and later hyaline membrane disease that required ventilation. We suggest that pressures of more than than 30 cm H₂O may be helpful during initial resuscitation and that there should be further study of devices using positive end expiratory pressure for resuscitation of preterm infants.</p>
Vyas 1981b	<p>Comment: Case series of asphyxiated term and preterm infants. Chest wall movement was used as criterion for adequate inflation. Maximum pressures of 33-73 cm H₂O (median 50); inspiratory time 0.5 sec.</p> <p><i>LOE 5; supports H3 and H4; neutral H5 and H6</i></p>
Vyas 1986	<p>Vyas, H., A. D. Milner, et al. (1981). "Physiologic responses to prolonged and slow-rise inflation in the resuscitation of the asphyxiated newborn infant." <i>J Pediatr</i> 99(4): 635-9.</p> <p>Measurements of thoracic volume, inflation pressure, and intrathoracic pressure have been recorded at the resuscitation of nine newborn babies. The initial inflation pressure was maintained for approximately five seconds which produced a twofold increase in inflation volume compared</p>

	<p>to standard resuscitation techniques and always led to formation of an FRC. When the inflation pressure was increased slowly over three to five seconds, the apparent opening pressure which occurred universally in square wave inflation was rarely seen.</p> <p>Comment: Series of nine patients in which prolonged inflation, with peak pressure set at 30 cm H₂O, either by "square wave" maintained for 5 seconds or by "slow-rise inflation" resulted in an increase in tidal volume when compared with previously published data. No controls in the present study. Initial breath only given for 5 seconds. Subsequent breaths with an inspiratory time of 1 second.</p> <p><i>LOE 5; supports H3 and H4</i></p>
Hoskyns 1987	<p>Vyas, H., A. D. Milner, et al. (1981). "Intrathoracic pressure and volume changes during the spontaneous onset of respiration in babies born by cesarean section and by vaginal delivery." <i>J Pediatr</i> 99(5): 787-91.</p> <p>We studied the first breath of newborn infants delivered by cesarean section. Inspiratory pressure and volume were found to be similar to those in infants born vaginally. However, the expiratory and delivery pressures were found to be smaller. Functional residual capacity was formed less frequently after cesarean section than in the vaginally delivered group.</p> <p>Comment: Case series examining pulmonary mechanics with the onset of spontaneous respiration in full term infants delivered by cesarean section (n =12) and by vaginal delivery (n = 21). Mean negative inspiratory pressure was similar between the two groups, 39.5-40 cm H₂O (range 12 – 80 cm H₂O).</p> <p><i>LOE 5; neutral H3</i></p>
Dawes 1968	<p>Vyas, H., D. Field, et al. (1986). "Determinants of the first inspiratory volume and functional residual capacity at birth." <i>Pediatr Pulmonol</i> 2(4): 189-93.</p> <p>We have investigated the pattern of pressure and volume changes that occur in vaginally delivered, full-term infants during the onset of spontaneous respiration. Within a few seconds of delivery of the head, simultaneous measurements were made of stomach and esophageal pressure changes together with volume changes determined at the mouth. Values obtained for volume were very similar, but pressure changes were of a greater magnitude than previously reported. A significant correlation has been shown between first inspiratory volume and functional residual capacity (FRC) at the end of the first breath (p less than 0.004). No significant relationship was found between first inspiratory pressure and FRC. However, using a calculated index of inspiratory pressure and time ("inspiratory effort"), a significant relationship of this to FRC was observed (p less than 0.02).</p>
Kattwinkel 1999	<p>Comment: Case series examining pressure and volume changes with the onset of spontaneous respiration in full term infants. No evidence of an opening pressure. 15/16 babies developed an FRC. Esophageal pressures ranged from –28 to –105 cm H₂O on inspiration (mean –52 cm H₂O). FRC correlated with inspiratory volume and inspiratory effort suggesting positive</p>

<p>Milner 1982</p> <p>Milner 1991</p> <p>Milner 1998</p>	<p>benefit of a sustained initial inflation.</p> <p><i>LOE 5; supports H3 and H4</i></p> <p>Hoskyns, E. W., A. D. Milner, et al. (1987). "Endotracheal resuscitation of preterm infants at birth." <i>Arch Dis Child</i> 62(7): 663-6.</p> <p>The adequacy of initial ventilation in 21 preterm babies (25-36 weeks' gestation), who required endotracheal intubation and positive pressure ventilation, were studied. Pressure and flow were measured at the proximal end of the endotracheal intubation tube and expiratory volume calculated from the flow trace. The results were compared with those from a group of 26 term infants who also required resuscitation. Five of 21 preterm babies (24%) had adequate tidal ventilation with the first inflation. This rose to seven of 21 (33%) by the third inflation. This was significantly less than the results in the term infants (chi 2 = 4.38 p less than 0.05). Respiratory reflex responses to resuscitation were seen in 41% of inflations in preterm and 56% of inflations in term infants. There was a significant correlation between reflex activity and adequate ventilation in the preterm group (chi 2 = 11.83, p less than 0.001) but not in the term group (chi 2 = 0.212, p = NS). No correlation was seen between initial ventilation and outcome.</p>
<p>Niermeyer 2000</p>	<p>Comment:</p> <p>Mean inflation pressure given to these preterm infants was 27 cm H2O.</p> <p><i>LOE 4; opposes H3</i></p> <p>Selected Reviews/Consensus Statements:</p> <p>Dawes G. S. (1968) "Birth asphyxia, resuscitation, and brain damage." In: <i>Foetal and Neonatal Physiology. A Comparative Study of the Changes at Birth</i>, edited by Dawes G. S. Chicago: Year Book Medical Publishers, Inc.</p> <p>Kattwinkel, J., S. Niermeyer, et al. (1999). "An advisory statement from the Pediatric Working Group of the International Liaison Committee on Resuscitation." <i>Pediatrics</i> 103(4): e56.</p> <p>The International Liaison Committee on Resuscitation (ILCOR), with representation from North America, Europe, Australia, New Zealand, Africa, and South America, was formed in 1992 to provide a forum for liaison between resuscitation organizations in the developed world. This consensus document on resuscitation extends previously published ILCOR advisory statements on resuscitation to address the unique and changing physiology of the newly born infant within the first few hours after birth and the techniques for providing advanced life support. After careful review of the international resuscitation literature and after discussion of key and controversial issues, consensus was reached on almost all aspects of neonatal resuscitation, and areas of controversy and high priority for additional research were delineated. Consensus on resuscitation for the newly born infant included the following principles: Common or controversial medications (epinephrine, volume expansion, naloxone, bicarbonate), special resuscitation circumstances affecting care of the newly born, continuing care of the newly born after resuscitation, and ethical considerations for initiation and discontinuation of resuscitation are discussed. There was agreement that insufficient data exist to</p>

recommend changes to current guidelines regarding the use of 21% versus 100% oxygen, neuroprotective interventions such as cerebral hypothermia, use of a laryngeal mask versus endotracheal tube, and use of high-dose epinephrine. Areas of controversy are identified, as is the need for additional research to improve the scientific justification of each component of current and future resuscitation guidelines.

Milner, A. D. and H. Vyas (1982). "Lung expansion at birth." J Pediatr **101**(6): 879-86.

Milner, A. D. (1991). "Resuscitation of the newborn." Arch Dis Child **66**(1 Spec No): 66-9.

Milner, A. D. (1998). "Resuscitation at birth." Eur J Pediatr **157**(7): 524-7.
It is only in recent years that the techniques used for resuscitation at birth have come under critical review and there have been very few controlled trials to assess their efficacy. Recent studies have indicated that the large majority of asphyxiated term babies can be resuscitated using air rather than 100% oxygen, possibly reducing damage from oxygen free radicals during re-perfusion. Physiological studies have shown that inflation pressures of 25-30 cm H₂O maintained for up to 1 s, only result in approximately 40% of the mean inspiratory volume achieved by babies who breathed spontaneously at birth. These spontaneous inflation volumes can be matched either by maintaining the first inflation for 3 s, or by using pressures of up to 50 cm H₂O for 300 ms, a pattern adopted by spontaneously breathing babies. Bag and mask systems are even less effective, often depending on the Head paradoxical reflex to stimulate respiration rather than producing adequate tidal exchange. Face mask T-piece devices provide more effective ventilatory exchange and are easier to use. CONCLUSION: Although the pattern of ventilatory support in current use often leads to successful resuscitation of asphyxiated babies at birth, more physiological and randomised controlled studies are needed to refine techniques in order to limit babies' exposure to potentially damaging hypoxia to the minimum.

Niermeyer, S., J. Kattwinkel, et al. (2000). "International Guidelines for Neonatal Resuscitation: An excerpt from the Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care: International Consensus on Science. Contributors and Reviewers for the Neonatal Resuscitation Guidelines." Pediatrics **106**(3): E29.

The International Guidelines 2000 Conference on Cardiopulmonary Resuscitation (CPR) and Emergency Cardiac Care (ECC) formulated new evidenced-based recommendations for neonatal resuscitation. These guidelines comprehensively update the last recommendations, published in 1992 after the Fifth National Conference on CPR and ECC. As a result of the evidence evaluation process, significant changes occurred in the recommended management routines for: * Meconium-stained amniotic fluid: If the newly born infant has absent or depressed respirations, heart rate <100 beats per minute (bpm), or poor muscle tone, direct tracheal suctioning should be performed to remove meconium from the airway. * Preventing heat loss: Hyperthermia should be avoided. * Oxygenation and ventilation: 100% oxygen is recommended for assisted ventilation; however, if supplemental oxygen is unavailable, positive-pressure ventilation should be initiated with room air. The laryngeal mask airway may serve as an effective alternative for establishing an airway if bag-mask ventilation is ineffective or attempts at intubation have failed.

Exhaled CO₂ detection can be useful in the secondary confirmation of endotracheal intubation. * Chest compressions: Compressions should be administered if the heart rate is absent or remains <60 bpm despite adequate assisted ventilation for 30 seconds. The 2-thumb, encircling-hands method of chest compression is preferred, with a depth of compression one third the anterior-posterior diameter of the chest and sufficient to generate a palpable pulse. * Medications, volume expansion, and vascular access: Epinephrine in a dose of 0.01-0.03 mg/kg (0.1-0.3 mL/kg of 1:10,000 solution) should be administered if the heart rate remains <60 bpm after a minimum of 30 seconds of adequate ventilation and chest compressions. Emergency volume expansion may be accomplished with an isotonic crystalloid solution or O-negative red blood cells; albumin-containing solutions are no longer the fluid of choice for initial volume expansion. Intraosseous access can serve as an alternative route for medications/volume expansion if umbilical or other direct venous access is not readily available. * Noninitiation and discontinuation of resuscitation: There are circumstances (relating to gestational age, birth weight, known underlying condition, lack of response to interventions) in which noninitiation or discontinuation of resuscitation in the delivery room may be appropriate.

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