Breathing patterns during cardiac arrest

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Surviving an out-of-hospital cardiac arrest (CA) depends on its immediate identification and treatment by cardiopulmonary resuscitation (CPR) (13, 36). However, to untrained bystanders, the recognition of CA based on the absence of cardiac beats or arterial pulsation can be difficult. To assist in the identification of CA, 911 call dispatchers have developed strategies (14, 29, 36, 38) for differentiating CA from other acute conditions that cause unresponsiveness (4, 9, 10, 14). Recently, an editorial (29) published in the Circulation journal proposed that the focus of lay rescuers attempting to discern the cause of unresponsiveness should be the pattern of breathing, with apnea (rather than pulselessness) being considered the cardinal sign of CA that should prompt the commencement of CPR. Even though empirical data for this recommendation are lacking, this approach is used by dispatchers who would not consider the diagnosis of CA in a patient with normal breathing (4). In other words, the presence of eupneic (normal) breathing is assumed to be incompatible with a diagnosis of CA.

These clinical considerations prompt a closer examination of what is known about the pattern of breathing during CA in humans. Previous work in which the breathing patterns during cardiac arrest have been described in animals have either overlooked this question or have simply assumed that any respiratory movements during a CA must be gasps (24, 28). Yet, from a physiological perspective, CA will certainly affect breathing control in various ways that may or may not lead to a rapid cessation of breathing. First, it seems unlikely that during a CA, brain stem PO2 will fall immediately to the critical level where anoxic apnea occurs and agonal breathing movements are generated (15, 26). Second, the immediate and profound decrease in arterial blood pressure (ABP) should stimulate breathing with no delay. This response has long been characterized (20): ventilation is stimulated within one breath when arterial pressure decreases abruptly, but then breathing adapts and returns toward baseline values (8, 18). This respiratory response is mediated by both arterial baroreceptors, responding to the decrease in carotid pressure, and arterial chemoceptors, which are exquisitely sensitive to the reduction in carotid flow (1, 8, 18, 39, 45). Third, the direct consequences of the drop in cerebral blood flow, resulting in brain stem acidosis, should yield a progressive stimulation of breathing until hypoxic apnea occurs (5, 6). Finally, and perhaps most importantly, the cessation of venous return to the pulmonary circulation, one of the fundamental mechanisms proposed to be involved in the coupling between breathing and pulmonary gas exchange, may produce apnea (for a discussion, see Ref. 46). Indeed, empirically derived information from animal models suggests that if the delivery of CO2 to the lungs ceases, breathing should promptly stop regardless of the composition of the arterial blood (23, 31). Although no clear control mechanism has been proposed to achieve such a finely calibrated blood gas homeostasis (16, 46), this latter mechanism may well provide a physiological basis for the contention that breathing stops along with the cardiac mechanical activity.

In summary, at the onset of CA we expect an immediate and brief stimulation of breathing followed after a few breaths by a rapid inhibition of respiration as a consequence of the lack of venous return to the lungs (3, 23), an inhibition that could be offset by a progressive medullary acidemia.

To document the effect of CA upon breathing patterns, we studied the ventilatory response to a CA in a group of eight human patients during ventricular fibrillation (VF). We then extended these observations in sheep to determine the change in ventilation until agonal breathing and ultimately apnea resulted. Finally, we sought to determine, in the same model, the critical level of oxygenation required to sustain regular
breathing to clarify the putative role of ischemia-induced brain stem anoxia during CA.

METHODS

Experiments in Humans

Subjects. Eight male subjects were studied. Their median age, height, and weight were 60 yr old (range: 32–71 yr old), 180 cm (range: 165–193 cm), and 96.2 kg (range: 68.6–113.4 kg), respectively.

VF protocol. All subjects underwent the subcutaneous placement of an implantable cardioverter-defibrillator device (ICD; Intrinsic DR ICD generator, Medtronic, Minneapolis, MN) for standard clinical indications under intravenous sedation with Propofol (dipropylphenol). In accordance with standard clinical protocols, the efficacy of the ICD was confirmed before the end of the procedure by the induction of VF (using high-frequency burst pacing, 50 Hz, 8 V), allowing for the appropriate discharge of the device to restore sinus rhythm. This interval between the induction of the VF and the discharge of the device afforded an opportunity to monitor ventilation for an interval in the range of 12–15 s. No alterations or modifications of the clinical procedures were made. All measurements were done in accordance with a protocol previously approved by the Institutional Review Board.

Measurements. The equipment used has been previously described in detail (19). Ventilation was recorded using a low-dead space small- or medium-sized face mask (7400 Oro-nasal series, Hans Rudolph, Kansas City, KS) connected to a turbine (model 17125, universal ventilation meter, VacuMed, Ventura, CA). Respiratory gas was continuously sampled for the measurement of the CO2 fraction by a fast-responding infrared analyzer (model 17630, VacuMed). In addition, systemic arterial pressure was determined noninvasively from the measurement of finger arterial pressure (Finapress system, Ohmeda, Louisville, LA). A Finapress cuff was placed around the index finger and connected to a Finapress monitor (model 2300, Ohmeda). Finally, the surface ECG signal was recorded. Respiratory flow, expired CO2, blood pressure, and ECG signals were digitized at 200 Hz (Power Lab system, AD Instruments) and displayed online using a microcomputer. The inspiratory flow signal was integrated to obtain tidal volume from the total breath cycle duration, breathing frequency, inspired minute ventilation, and end-tidal Pco2, all on a breath-by-breath basis.

Data analysis. Baseline breathing parameters were determined by measuring the five breaths preceding the onset of CA. Data were averaged, and baseline data were compared with the period of CA for each test using a paired t-test.

Experiments in Sheep

Animal preparation. Nine sheep (43.0 ± 4.6 kg) were studied. All procedures were approved by the Pennsylvania State University College of Medicine Institutional Animal Care and Use Committee. Sheep were premedicated with ketamine (40 mg/kg im), with subsequent anesthesia induced with a loading dose of pentobarbital sodium (6 mg/kg iv). Sedation was maintained throughout the experiment using a urethane (25%, 30 mg/kg iv) and α-chloralose (5%, 150 mg/kg iv) solution (17). Animals were tracheotomized. A catheter was introduced into the left carotid artery to monitor ABP and arterial blood gas sampling. Another catheter was placed in the right external jugular vein for injections of anesthetic agents. At the termination of the experimental procedure, sheep were euthanized with pentobarbital sodium (200 mg/kg) and potassium chloride (−9 meq/kg) injected intravenously.

Measurements. Animals breathed through a two-way valve (1420 Series, Hans Rudolph) coupled to the tracheal cannula via a calibrated pneumotachograph (Fleisch No. 2, Phipps and Bird). Respirated CO2 was analyzed using a fast-responding infrared analyzer (model 17630, Vacumed). ABP was continuously recorded using a pressure transducer (model MLT0380/D, AD Instruments). All signals were collected with an analog-to-digital data-acquisition system (Powerlab 16/30, ML880, AD Instruments) at a rate of 200 Hz.

VF protocol. In four sheep, a 7-Fr ICD lead (Endotak Reliance G 0185, Boston Scientific) was advanced into the right ventricle. The tip of the lead was then screwed into the myocardium. A Medtronic Intrinsic DR ICD generator was implanted subcutaneously. VF was induced using high-frequency burst pacing (50 Hz, 8 V) delivered for 1–4 s. The induction of VF was confirmed by the ventricular electrogram and surface ECG. VF was terminated by delivering a 20-J biphasic direct current shock.

Anoxic exposure. In the five remaining sheep, the inspiratory port of the valve was switched from room air breathing to 100% nitrogen (see Protocol below).

Protocol. VF. After a period of at least 15 min of quiet and stable breathing, VF was induced and maintained until breathing stopped and a first gasp occurred. In most tests, VF was terminated after the two first gasps after a period of apnea.

ANOIC EPISODES. After a period of at least 15 min of quiet and stable breathing, anoxic exposure was applied and maintained until ventilation stopped; the animal was then switched back to air.

Data analysis. The flow signal was integrated for breath-by-breath measurements of tidal volume, breathing frequency, and minute ventilation in body temperature pressure saturated conditions. The onset of apnea and onset of the first gasp were calculated. Baseline data were computed over the last 30 s preceding VF and were compared with the entire period during which breathing persisted using a paired t-test. All data are expressed as means ± SD.

For the anoxic exposure, arterial blood gases were also measured (Bayer Rapidlab 865, Siemens Healthcare Diagnostics) before anoxic exposure, at the precise moment that ventilation stopped, when the first gasp was produced, and when ventilation resumed spontaneously. ANOVA with repeated measurement was used to compare the change in arterial blood gases.

RESULTS

Experiments in Humans

A total of 11 episodes of CA ranging from 12 to 15 s were produced: 5 patients had 1 episode of VF, whereas 3 patients had 2 episodes each. Each episode of CA was analyzed as a separate event. Baseline mean breathing frequency was 17 ± 4 breaths/min, allowing the study of an average of four breaths. Figure 1A shows a representative example of the circulatory and ventilatory responses to an episode of CA. As expected, the onset of CA produced an immediate loss of the ABP signal. However, the pattern of breathing was unchanged. As shown in Fig. 1B, for the group, there were no changes in the frequency of breathing, tidal volume, or inspiratory and expiratory durations.

Experiments in Sheep

CA. A total of eight episodes of VF were produced. The interval between the two episodes of VF was a minimum of 30 min, by which point all ventilatory and circulatory measurements, including the measured arterial pH, were reestablished at baseline levels.

The onset of CA was associated with an abrupt drop in ABP from 122.7 ± 6.9 to 9–14 mmHg. Similar to the breathing pattern during VF in humans, no changes were evident during the first 15 s of CA (Figs. 2 and 3). Subsequently, ventilation began to increase (from 8.79 ± 3.91 to 16.52 ± 11.25 l/min,
\( P < 0.01 \), primarily due to increments in the tidal volume with little change in breathing frequency (18.2 ± 3.6 vs. 19.2 ± 4.3 breaths/min, not significant), as shown in Fig. 2. Altogether, this regular breathing pattern was maintained for 55 ± 44 s (range: 28–164 s) and then stopped abruptly. During this interval, end-tidal \( PCO_2 \) decreased by half (Figs. 2 and 3). Agonal breathing efforts [gasps (large breaths of short duration occurring at very low frequency)] were observed starting 37 ± 38 s into the apneic period (Fig. 3). The persistent respiratory activity during CA was associated with an increase (during expiration) and decrease (during inspiration) of ABP that produced maximal swings in carotid pressure totalling 27 ± 17 mmHg in phase with the breath cycles (Fig. 4). In many instances, a sharp positive inflection in blood pressure was
observed at the onset on expiration. When breathing movements stopped, mean ABP dropped toward the “mean filling pressure” within 30 s (Fig. 4).

Anoxic exposure. A total of 10 anoxic episodes were studied in 5 sheep. As during CA, the ventilatory changes during anoxic exposure could be divided into three phases: 1) maintenance of eupnea with an increase in breathing followed by 2) apnea and then 3) the production of gasps (Fig. 5). Indeed, after pure nitrogen exposure, minute ventilation increased from the control value of 9.10 ± 2.83 to 26.76 ± 4.19 l/min. This...
increase in ventilation was followed by reductions in both breathing frequency and tidal volume for a few breaths before the onset of apnea, which occurred 85.94 ± 9.07 s (range: 71.5–97.5 s) into the anoxic exposure. This initial apnea lasted 48.50 ± 17.68 s (range: 13.1–74.3 s), after which a single large breath (gasp) occurred.

In every test, with no exception, rhythmic activity resumed spontaneously after two to three gasps (nitrogen exposure was switched to room air at the onset of apnea; see METHODS). The interval between the onset of apnea and the restoration of a normal eupneic breathing pattern averaged 94.68 ± 21.17 s (range: 57.0–130.5 s).

The level of arterial PO2 (PaO2) at which breathing stopped averaged 15.56 ± 0.99 mmHg (baseline value of 64.01 ± 5.18 mmHg, P < 0.01), reaching a value of 12.95 ± 1.75 mmHg at the onset of the first gasp. The gasps that occurred during apnea were effective in reoxygenating the blood as PaO2 increased to 23.89 ± 4.02 mmHg when breathing resumed. Finally, arterial Pco2 (PaCO2) decreased from the preanoxia baseline of 37.26 ± 5.05 to 23.97 ± 5.05 mmHg (P < 0.01) at the onset of apnea. At the onset of the first gasp, PaCO2 had increased to 29.80 ± 5.90 mmHg, with a further increase at the restoration of rhythmic breathing (35.51 ± 6.26 mmHg, not significant from baseline).

DISCUSSION

In contrast to what we expected, we found that the ventilation of sedated spontaneously breathing humans is unaltered during a CA lasting up to 15 s. In addition, anesthetized spontaneously breathing sheep can sustain a regular ventilatory pattern for as long as 164 s after the complete cessation of cardiac pumping activity. Taken together, these observations represent compelling evidence that eupneic breathing persists at the onset of CA, suggesting a complete “decoupling” of effective respiratory activity from the rate of venous return to the lungs. These results clearly illustrate that the loss of respiratory activity is a very poor surrogate marker of CA, in contrast to most recommendations (4, 29). The present data also challenge the teleological view that respiration is controlled directly or indirectly by the gas exchange function of the lungs in all situations.

Eupneic Breathing Is Maintained After CA

The persistence of eupneic breathing should be clearly distinguished from the generation of gasps, which were produced well after apnea occurred (see Figs. 2 and 3). Gasps have very specific characteristics (11), consisting of short and brisk inspiratory and expiratory activity (35). They are produced with a slow and episodic pattern, very different from the rhythmicity of eupneic breathing (41–43).

In the absence of medullary blood flow during CA, the decrease in brain stem O2 is to be dictated by the local rate of O2 consumption and the amount of O2 available (40). The critical O2 level needed to stop the activity of respiratory neurons (15, 26) to produce gasps is unlikely to be reached immediately. Although a CA creates a very different condition than an anoxic exposure, we found that in the latter, eupnea was present until a very low level of PaO2 (15–17 mmHg). Gasps were produced at a PaO2 of ~12 mmHg, which must have corresponded to an even lower PO2 at the medullary level. It is therefore reasonable to assume that a cessation of breathing related to brain stem anoxia during a CA is unlikely to occur as soon as systemic (cephalic) blood flow drops.

As presented in the Introduction, there are many hypothetical counteracting mechanisms that may stimulate or inhibit breathing at the onset of a CA. The stimulation comprises the immediate and brief effects of the reduction in ABP on arterial baroreflexes and chemoreflexes (18, 39) as well as the medullary acidosis (25) secondary to the lack of brain stem blood flow. While the latter should develop progressively with time, the former should affect breathing within one breath (1, 8, 18, 45). Breathing should, however, quickly return toward baseline...
as the arterial baroreflex response has been shown to rapidly adapt (8, 18). The effects of the reduction in blood pressure (and carotid body blood flow) are far from negligible; in a similar sheep model where the cephalic circulation was isolated from the rest of the body, we (18) found that ventilation increases immediately by 200–600 ml/min for every 10–mmHg drop in cephalic perfusion pressure (18). This was obviously not the case during a CA, where ABP dropped immediately with no change in breathing for several breaths (Fig. 2).

Perhaps even more intriguing is the fact that ventilation persisted at the same level and even increased despite an absence of CO2 pulmonary blood flow. This clearly contradicts series of experimental data suggesting a strong matching or coupling between CO2 pulmonary blood flow and respiratory control (3, 22, 23). The fact that breathing was affected only after a delay does not support the view that respiratory rhythm control (3, 22, 23). The fact that breathing was affected only after a delay does not support the view that respiratory rhythm control (3, 22, 23). The fact that breathing was affected only after a delay does not support the view that respiratory rhythm control (3, 22, 23). The fact that breathing was affected only after a delay does not support the view that respiratory rhythm control (3, 22, 23).

The dramatic decrease in alveolar PCO2 after a CA deserves some mention (see Figs. 2 and 3). Bartoli et al. (2) suggested that in the dog, alveolar hypocapnia could contribute to the stimulation of breathing by increasing breathing frequency through a vagal feedback. The possible contribution and role of such a mechanism during a CA, when the persistence of ventilatory activity produces a dramatic reduction in alveolar CO2, needs to be explored.

Finally, the possible influence of the sedation on the observed respiratory responses should be acknowledged, as wakefulness is usually regarded as a “stimulus” to breathe (21, 34).

Blood Pressure Changes While Breathing During CA

Significant swings in ABP, in phase with the respiratory movements, were observed during CA. These changes in ABP are undoubtedly primarily related to the fluctuations in intrathoracic pressures akin to the mechanisms that produce blood pressure changes during the chest compressions of CPR. Whether these low-amplitude, low-frequency swings in blood pressure might generate some systemic blood flow, as shown during gasping (27, 37, 44), remains to be demonstrated. Indeed, the production of cerebral blood flow has been shown to be produced by agonal respiratory movements (37, 44). Interestingly during the period of hyperventilation before apnea, the magnitudes of respiratory flows and volumes were similar between augmented breaths and gasps (Fig. 3); whether some systemic flow was produced during this period of eupneic breathing remains an unanswered question. If true, however, the generation of breathing movements during CA may have contributed to the self-preservation of the activity of the respiratory central pattern generation of breathing by maintaining a small but significant perfusion of the cerebral vasculature.

Clinical Implications

These results clearly illustrate that the loss of respiratory activity is an inappropriate surrogate marker of the onset of a CA, despite recent recommendations that suggest otherwise (4, 29). For a lay bystander, many confounding factors can delay the recognition of such an out-of-hospital CA (14, 29, 36). The absence of “normal” regular respiratory movements has been currently proposed as the best surrogate marker of CA (4), implying that a CA must always be associated with a respiratory arrest, only interrupted by gasping events (7, 12, 38). In other words, it has been proposed that the diagnosis of CA should not be considered unless normal breathing is absent (7).

In a recent report, Berdowski et al. (4) analyzed emergency dispatch voice recordings for CA calls. They found that when callers mentioned the presence of breathing without any further description, the recognition of CA was delayed by half a minute since dispatchers were looking for other signs that could indicate a CA. From the present results, it is clear that the respiratory response to a CA is more complex than traditionally assumed. At the initial phase of a CA, when the chances of success of CPR are the highest, normal breathing is present, reducing the chance of rapidly identifying a CA. Once apnea has occurred and is associated with the generation of gasps, a very low level of medullary Po2 is likely to be already present.

We conclude that, at the onset of a CA, the respiratory neurons continue to generate normal breathing activity, despite the absence in pulmonary blood flow/cardiac output, which divorces breathing from its primary purpose of controlling pulmonary gas exchange. Therefore, in the early stages of a CA, the criteria for the correct diagnosis of CA should not include the absence of normal breathing movements.

REFERENCES

No conflicts of interest, financial or otherwise, are declared by the author(s).

BREATHING AND CARDIAC ARREST


