Breathing during cardiac arrest following exercise: A new function of the respiratory system?

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ABSTRACT

We have found in four sheep that, following a muscular exercise, minute ventilation is maintained for 34–131 s during a cardiac arrest (CA), at a magnitude (from 28.2 and 54.7 l min^{-1}) similar to the level of ventilation (and thus proportional to the metabolic rate) preceding the period of asystole. Breathing was maintained despite the lack of pulmonary blood flow and the cessation of the muscle contractions, leading to a dramatic reduction in alveolar FCO_2 ($1.9 \pm 1\%$). Secondly, swings in arterial blood pressure (ABP) were observed (pulse pressure of 31 ± 3 Torr) in phase with breathing movements in place of the cardiac activity. This "protective" response, deprived from any role in blood gas homeostasis, as circulation is virtually abolished, is not predictable from the traditional respiratory control feedback systems thought to be involved in exercise. We are presenting the view that this response, dissociated from the pulmonary gas exchanges, is the expression of a rudimentary defense mechanism aimed at limiting the consequences of an acute failure of the cardiac pump by the thoraco-abdominal pump.

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1. Introduction

One of the most fundamental and still poorly understood characteristics of breathing control is certainly its ability to "track and match" the level of metabolic activity. Such a coupling is maintained in keeping with the inter-species and intra-species differences in body size and metabolism (Frappell et al., 1992; Mortola, 1993, 2004), or following any increase in metabolic rate during a physical activity (Dejours, 1963; Whipp et al., 1982, 1984; Whipp and Ward, 1990, 1991; Dempsey et al., 1997).

We have recently shown that at the onset of a cardiac arrest (CA), fundamental physiological responses are still expressed (Haouzi et al., 2010), limiting transiently the effects of the absence of the cardiac contractions. The most intriguing of these responses is certainly the persistence of the normal activity of the thoraco-abdominal pump: in sedated sheep, the generation of normal breath cycles is maintained at the onset of a cardiac arrest for 40 s up to 2 min, despite the absence of flow generated by the heart (Haouzi et al., 2010). We also found that breathing is maintained unchanged in humans during the transient periods of an experimental fibrillation induced CA while testing implantable defibrillators (Haouzi et al., 2010). This breathing activity should not be confused with

the production of gasps (Guntheroth and Kawabori, 1975; Duffin, 2003; Eisenberg, 2006; Bobrow et al., 2008; Haouzi et al., 2010), with their unique and specific breathing pattern, which occur much later along with an apnea. Incidentally, this makes breathing an inappropriate surrogate marker of CA (Berdowski et al., 2009).

The major consequence of this observation relates to the fundamental physiological mechanisms, meaning, and implications of the maintenance of a normal breathing activity with no circulation. The challenge, which we could not resolve in our previous report, was to reconcile the known effects of the main feedback systems affecting breathing control during a CA with the actual breathing pattern we observed (Haouzi et al., 2010). These feedbacks comprise the respiratory effects of an abrupt cessation of pulmonary blood flow/cardiac output and arterial CO_2 oscillations along with the consequences of a drop in blood pressure and in cerebral blood flow.

The goal of this study was to establish the relationship between the activity of the central pattern generator of breathing, in a "no-flow" situation, following a muscular exercise wherein the metabolic/ventilatory levels are increased (Whipp and Ward, 1991; Haouzi, 2006). The question is whether ventilation can be maintained as at rest despite the lack of blood flow and the cessation of muscle contractions; and if it is, at what level?

The hypothesis we are testing here is that there is a genuine, although rudimentary, adaptive response to conditions of very low or no blood flow, which has been overlooked, as this response cannot be predicted from the properties of traditional feedback systems when considered separately. For all these reasons, how

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breathing is affected at the onset of a cardiac arrest following exercise remains an outstanding question.

In the present study, the ventilatory, gas exchange and arterial blood pressure (ABP) responses were determined breath-by-breath during VF induced CA following electrically induced muscle contractions of the hindlimbs in sedated spontaneously breathing sheep (Haouzi and Chenuel, 2005; Haouzi et al., 2010).

2. Methods

We have previously reported the ventilatory responses following a cardiac arrest in resting conditions (Haouzi et al., 2010). In this previous study, every episode of ventricular fibrillation was terminated by delivering a 20 J biphasic DC shock upon the third gasp following respiratory arrest. This allowed us to produce several episodes of cardiac arrest at rest in the same animal, in the course of a 4–5 h study, as we found that breathing returned to baseline within less than 20 min, with rapidly reversible change in arterial pH. The following protocol was applied in 4 of these animals.

2.1. Animal preparation

Four sheep (43–55 kg) were pre-medicated with ketamine (40 mg kg^{-1}, IM), with subsequent anesthesia induced with a loading dose of sodium pentobarbital (6 mg kg^{-1}, iv). Procedures were approved by the local Institutional Animal Care and Use Committee. Sedation was maintained throughout the experiment using urethane (25%, 30 mg kg^{-1}, IV) and α-chloralose (5%, 150 mg kg^{-1}, IV) solution. Animals were tracheotomized, and a catheter was introduced into the left carotid artery to monitor arterial blood pressure. Another catheter was placed in the right external jugular vein for injections of anesthetic agents. At the termination of the experiment, sheep were euthanized with sodium pentobarbital (200 mg kg^{-1}) and potassium chloride (∼9 meq kg^{-1}) injected IV.

2.2. Measurements

Animals breathed through a two-way valve (1420 Series, Hans Rudolph, KS, USA), coupled to the tracheal cannula via a calibrated pneumotachograph (Fleisch No. 2, Phipps and Bird, VA, USA). Expired CO_2 was analyzed using a fast responding infrared analyzer (model #17630, Vacumed, Ventura CA, USA). Oxygen uptake was determined from the measurement of mixed expired O_2 fraction collected in an expiratory bag (model #17630, Vacumed, Ventura CA, USA) along with the corresponding level of expired minute ventilation. Arterial carotid BP was continuously recorded using a pressure transducer (Model MLT0380/D, AD Instruments, CO, USA). The transducer was calibrated before each experiment using a mercury column. All signals were collected with an analog–digital data acquisition system (Powerlab 16/30, ML880, AD Instruments, CO, USA) at a rate of 200 Hz.

2.3. Fibrillation protocol

A 7 French ICD lead (Boston Scientific, Endotak Reliance G 0185) was advanced into the right ventricle. The tip of the lead was then screwed into the myocardium. A Medtronic Intrinsic DR ICD generator (Medtronic, Inc., Minneapolis, Minnesota) was implanted subcutaneously. VF was induced using high-frequency burst pacing (50 Hz, 8 V). Induction of ventricular fibrillation was confirmed by the surface ECG.

2.4. Muscle contractions prior to CA

The hindlimbs were shaved, and two pairs of large electrodes with conductive gel were placed on both thighs. Muscle contractions were generated using a modulated stimulation frequency of 40 Hz, applied for 2 s every 4 s. Current intensity was set to between 10 and 15 mA with a rise and fall time of 0.5 s. Muscle contractions during this stimulation protocol produced a rhythmic extension and adduction of the hindlimbs resembling dynamic exercise. The contractions were performed against a resistance consisting of rubber bands attached to the distal part of the limbs and were of sufficient intensity to at least double minute ventilation and metabolism (Haouzi and Chenuel, 2005).

2.5. Protocol

After a period of at least 15 min of quiet and stable breathing, at least 30 min after a previous FV, contractions were produced and maintained for 5 min prior to experimental CA and terminated upon initiation of VF.

Ventricular fibrillation was terminated by delivering a 20 J biphasic DC shock upon the first gasps following respiratory arrest.

2.6. Data analysis

Data were analyzed offline using Chart software (ADInstruments). The flow signal was integrated for breath-by-breath measurement of tidal volume (V_T), and derived for the determination of gas acceleration. Breathing frequency and minute ventilation (in BTPS conditions) were determined breath-by-breath. All data are expressed as individual results (in the figures) and as mean ± SD or the median.

Each cardiac arrest was analyzed as a separate event. The arterial blood pressure and ventilatory parameters were analyzed during the last minute of exercise preceding the CA and during the entire period of cardiac arrest when eupneic breathing was maintained. Data were compared using Wilcoxon signed-ranked tests, $p < 0.05$ was regarded as significant.

In our previous report (Haouzi et al., 2010), we were surprised to see that ABP did not appear to follow the change in lung volume (and thus the expected change in trans-pulmonary pressure). We therefore analyzed the change in ABP more systematically in keeping with the respiratory cycle (inspiration and expiration) as follows: the total pressure produced by the respiratory system at a time t ($Prs(t)$) to mobilize a volume V at a flow V', and an acceleration V'' can be regarded as the sum of the elastic pressure (proportional to the elastance (E) and the volume of gas mobilized (V)), the resistive pressure (proportional to the resistance (R) and the flow of gas mobilized (V')) and inertial pressure (proportional to the inertia (I) and the acceleration of gas mobilized): $Prs(t) = E \cdot V(t) + R \cdot V'(t) + I \cdot V''(t)$. The multivariate linear equation was therefore computed between ABP, V, V' and V'' to determine the relative weight of each of the 3 respiratory variables in the generation of ABP. Four parameters were therefore obtained, three proportional to V, V' and V'' respectively and one corresponding to mean ABP. Computations were performed on 3 consecutive breaths at the peak of the oscillations in ABP during a given episode of CA.

3. Results

3.1. Effects of muscle contractions

An example of the response to electrically induced muscle contractions is shown in Fig. 1. Responses were identical