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EXPERIMENTAL PAPER

# Spontaneous gasping decreases intracranial pressure and improves cerebral perfusion in a pig model of ventricular fibrillation<sup>☆</sup>

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## KEYWORDS

Cardiac arrest;  
Gasping;  
Intracranial pressure;  
Cerebral perfusion;  
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## Summary

**Introduction:** Spontaneous gasping is associated with increased survival in animal models of cardiac arrest and in observational studies of humans. The potential beneficial effect of gasping on cerebral perfusion may underlie the observed survival benefit, but mechanisms remain unknown.

**Hypothesis:** We hypothesized that spontaneous gasping in a pig model of ventricular fibrillation (VF) decreases intracranial pressure (ICP) and increases cerebral perfusion pressure (CePP) during VF in a pig model.

**Methods:** The 13 female farm pigs, weighing between 16 and 33 kg, were anesthetized with propofol and intubated, and then had VF induced for 8 min without intervention. Intrathoracic pressure (ITP), aortic pressure (AoP), and ICP were measured continuously. CePP and ITP were recorded simultaneously during three maximal gasps and correlated with gasping by Spearman rank correlation.

**Results:** Gasping during VF occurred in 13/13 pigs and followed a crescendo-decrescendo pattern. Each gasp was associated with a biphasic AoP (initial fall, then rise) and ICP (initial rise, then fall) morphology. Time to first gasp ( $r^2 = 0.06$ ), time to maximal gasp ( $r^2 = 0.02$ ), duration of gasping ( $r^2 = 0.11$ ) and frequency of gasping ( $r^2 = 0.32$ ) did not correlate significantly with CePP during gasping while depth of gasping exhibited a weak but significant correlation with CePP ( $r^2 = 0.35$ ,  $p = 0.05$ ). Maximal gasping occurred at  $202 \pm 34$  s from onset of VF and resulted in an average

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decrease in ICP from  $27.4 \pm 5.8$  to  $20 \pm 6.7$  mmHg,  $p < 0.01$  along with an increase in CePP from  $-0.05 \pm 10.9$  to  $11.5 \pm 12.6$  mmHg,  $p < 0.05$ .

**Conclusions:** Spontaneous gasping during cardiac arrest decreased intra-cranial pressure and increased cerebral perfusion pressure significantly. These results may help explain why gasping is associated with improved cardiac arrest survival rates. Based upon this new understanding of the physiology of gasping, we speculate that investigation of devices that can enhance the physiological effects of gasping on intracranial pressure and cerebral perfusion should be prioritized.

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## Introduction

Several physiologic phenomena such as gasping, coughing, Valsalva and Müller maneuvers are associated with reanimation following cardiac arrest.<sup>1</sup> Gasping is especially unique since it has been observed to occur universally in mammals at the beginning and at the end of life.<sup>2</sup> Previous studies in different animal models have demonstrated that gasping is associated with improved upper airway patency,<sup>3</sup> improved pulmonary gas exchange during cardiopulmonary resuscitation in the setting of cardiac arrest<sup>4,5</sup> and generation of cardiac output during cardiac arrest.<sup>6</sup> These mechanisms are believed to underlie the association of spontaneous gasping with increased survival in animal models of cardiac arrest<sup>4,5</sup> and in observational studies of humans.<sup>7–10</sup> The potential beneficial effect of gasping on cerebral blood perfusion may be another contributing factor to the observed survival benefit, but mechanisms remain unknown. We hypothesized that spontaneous gasping decreases intracranial pressure (ICP) and increases cerebral perfusion pressure (CePP) during ventricular fibrillation (VF) in a pig model.

## Materials and methods

The Committee on Animal Experimentation approved this project at the University of Minnesota. All animals were managed in accordance with the guidelines of the American Physiological Society, the University of Minnesota, and the position of the American Heart Association on Research Animal Use. Qualified individuals supervised animal care and use, and all facilities and transportation complied with current requirements and guidelines. Anesthesia was used in all surgical interventions. All unnecessary suffering was avoided, and research was terminated if unnecessary pain or suffering resulted. Our animal facilities meet the standards of the American

Association for Accreditation of Laboratory Animal Care.

## Preparatory phase

The study was performed according to Utstein-style guidelines<sup>11</sup> on 13 healthy, 12–16 week old female domestic farm pigs weighing 16–33 kg. The pigs were sedated with 5–7 ml (100 mg/ml) of intramuscular ketamine HCl (Ketaset®, Fort Dodge Animal Health, Fort Dodge, IA) and anesthetized with propofol (PropoFlo®, Abbott Laboratories, North Chicago, IL) intravenous (IV) bolus (2–3 mg/kg) via an ear vein. The trachea was intubated with a 7.5-mm cuffed tracheal tube (Mallinckrodt Critical Care, Glens Falls, NY) while the pigs were sedated and breathing spontaneously. Titrated anesthesia was maintained for the duration of the study by means of a propofol infusion of 160 µg/kg/min guided by prospectively set target parameters for heart rate, blood pressure, tail and hoof pinch response, and spontaneous breathing. The pigs were provided mechanical ventilation (Model 607; Harvard Apparatus Co., Dover, MA) until breathing spontaneously following initial anesthesia at a volume-controlled setting of 20 ml/kg. During the preparation time, respiratory frequency was adjusted at 10–12 breaths/min to maintain the mean end-tidal carbon dioxide pressure at 35–40 mmHg; inspiratory oxygen concentration was titrated to maintain oxygen saturations of >96% measured via pulse oximetry.

A small 5-mm diameter burr hole craniotomy was created on the left side to place an intracranial pressure-monitoring device. After identifying the vertex of the cranium, a craniotomy was performed at the middle of a line between the left eyebrow and the vertex. A single high-fidelity micromanometer-tipped epidural catheter (Millar Instruments, Houston, TX) pressure transducer was inserted 3 cm under the skin, approximately 2 cm into the parietal lobe of the animal and secured in place with cement and sutures. The pressure

transducer was connected with a digital acquisition and recording system (Superscope II®, v1.295, GW Instruments, Somerville, MA) giving real time ICP tracings.

Subsequently, animals were positioned supine and the left femoral artery was cannulated via a cut-down to place a micromanometer-tipped catheter (Mikro-Tip® Transducer, Millar Instruments Inc., Houston, TX) to record central aortic blood pressures continuously 45 cm from skin insertion. A central venous catheter was placed in the right external jugular vein and advanced 10 cm into the proximal superior vena cava to record central venous and right atrial pressures. All animals were treated with a bolus dose of heparin (100 units/kg IV), once catheters were in place. Intrathoracic pressures were measured and recorded continuously using a micromanometer-tipped catheter positioned 2 cm below the tip of the tracheal tube.

## Experimental protocol

Once the surgical preparations were completed, and the oxygen saturation was >96% and the end-tidal carbon dioxide stable between 35 and 40 mmHg for 5 min, prearrest hemodynamic variables were recorded. VF was induced by delivering a 50 Hz, 7.5 V AC electrical current via a temporary pacing wire positioned in the right ventricle. All animals remained in VF with no pulsatile blood pressure for the full 8 min non-intervention period. After 8 min of untreated VF, the animals were resuscitated according to the standard laboratory protocol conforming to ACLS guidelines. At the end of the protocol, the animals were killed humanely using a large intravenous bolus of propofol (200 mg) followed by potassium chloride solution (10 M).

## Measurements

Pressure tracings obtained from the high-fidelity micromanometer catheters were continuously monitored with a data acquisition (Superscope II v1.295, GW Instruments, Somerville, MA) and computerized recording system (Apple Macintosh). Digitized data were analyzed electronically to provide hemodynamic measurements. Heart rate was determined from a simultaneously recorded electrocardiogram signal. Aortic pressure (AoP), intracranial pressure (ICP) and intrathoracic pressure (ITP) were simultaneously recorded during three maximal gasps during VF cardiac arrest. Cerebral perfusion pressure (CePP) during normal perfusion was calculated as the difference between mean AoP and ICP, while CePP during gasping in VF

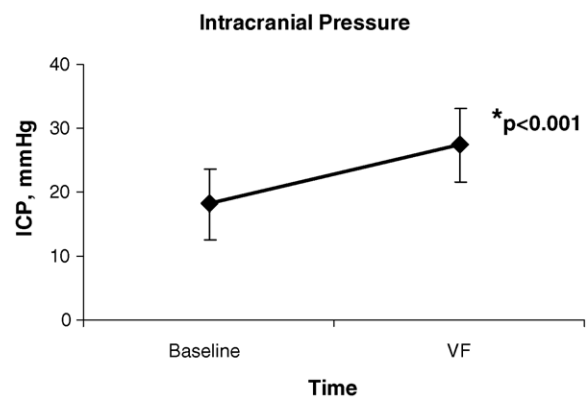
was calculated as the time-coincident difference between maximum AoP and ICP.

## Statistical analysis

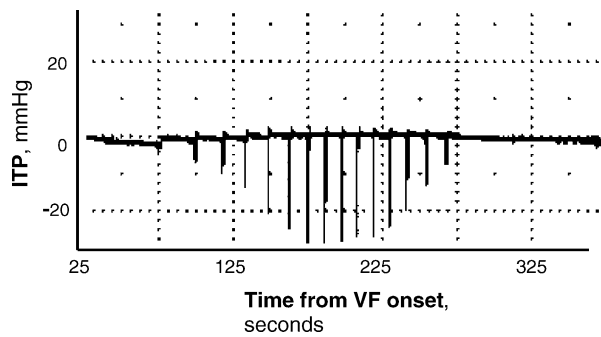
The primary outcome variable was selected prospectively as the change in CePP with gasping during VF cardiac arrest. Other outcome variables analyzed included change in ICP with gasping during VF cardiac arrest. Descriptive characteristics of gasping including time to first gasp, duration of gasping, frequency of gasping and depth of gasping were correlated to CePP during gasping by Spearman rank correlation. Multiple comparisons between groups were performed with one-way analysis of variance. All values are expressed as mean  $\pm$  S.D. where appropriate. Results were considered to be statistically significant if  $p < 0.05$ .

## Results

With onset of VF, ICP increased from  $18.1 \pm 5.5$  to  $27.4 \pm 5.8$  mmHg ( $p < 0.001$ ) (Figure 1) and CePP decreased from  $73.6 \pm 12.1$  to  $-0.05 \pm 10.9$  mmHg ( $p < 0.001$ ). Gasping during VF occurred in 13/13 pigs and followed a crescendo–decrescendo pattern (Figure 2). Each gasp was associated with a biphasic AoP (initial fall, then rise) and ICP (initial rise, then fall) morphology (Figure 3) with time to first gasp  $88.5 \pm 33.4$  s, duration of gasping  $194.6 \pm 58.5$  s, frequency of gasping  $5.4 \pm 0.9$  gasps/min, and depth of gasping  $-22.8 \pm 8$  mmHg. Time to first gasp ( $r^2 = 0.06$ ), time to maximal gasp ( $r^2 = 0.02$ ), duration of gasping ( $r^2 = 0.11$ ) and frequency of gasping ( $r^2 = 0.32$ ) did not correlate significantly with CePP during gasping while depth of gasping exhibited a weak but significant correlation with CePP ( $r^2 = 0.35$ ,



**Figure 1** Increase in intracranial pressure (ICP) with onset of ventricular fibrillation (VF).

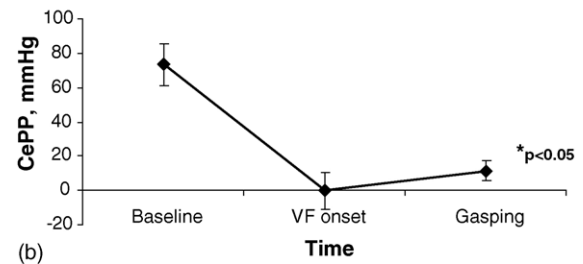
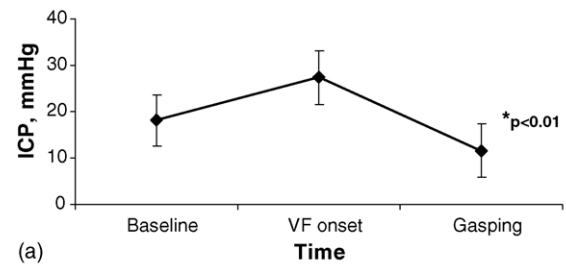


**Figure 2** A representative tracing of intra-thoracic pressures reflecting the crescendo-decrescendo pattern of gasping observed during ventricular fibrillation (VF).

$p=0.05$ ). Maximal gasping occurred at  $202 \pm 34$  s from onset of VF and resulted in decrease in ICP from  $27.4 \pm 5.8$  to  $20 \pm 6.7$  mmHg,  $p < 0.01$  along with increase in CePP from  $-0.05 \pm 10.9$  mmHg to  $11.5 \pm 12.6$  mmHg,  $p < 0.05$  (Figure 4).

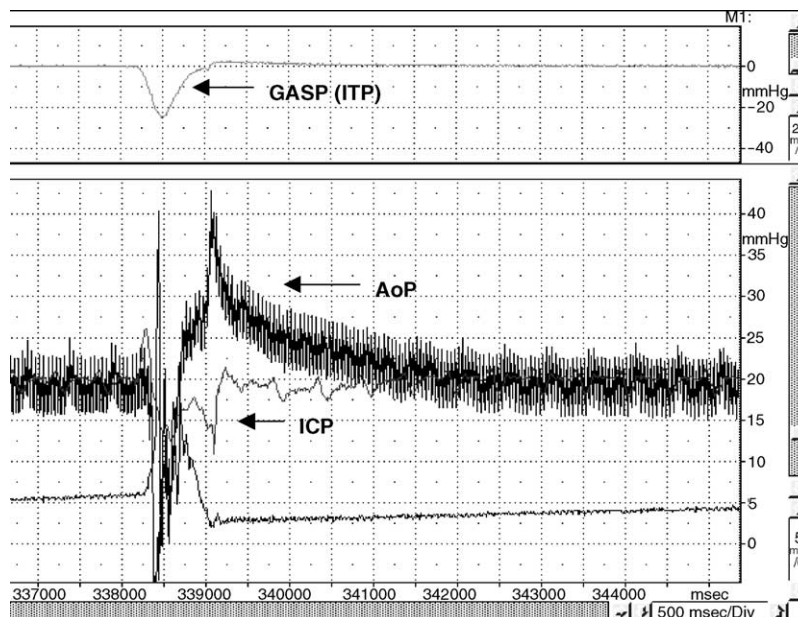
## Discussion

Gasping is a very well-known phenomenon, having been first described in 1812 by Legallois.<sup>12</sup> In 1923, Lumsden demonstrated the occurrence of gasping in response to progressive hypoxia and sequential depression of brain stem respiratory centers. He speculated that gasping might be a fundamental reflex associated with auto-resuscitation, and thus be an essential evolutionary mechanism



**Figure 4** (a) Fall in intracranial pressure (ICP) and (b) rise in cerebral perfusion pressure (CePP) with maximal gasping during ventricular fibrillation (VF).

across species.<sup>13,14</sup> Since then, several studies in different animal models have demonstrated that gasping is associated with improved upper airway patency,<sup>3</sup> improved pulmonary gas exchange during cardiopulmonary resuscitation in the setting of cardiac arrest<sup>4,5</sup> and generation of cardiac output during cardiac arrest.<sup>6</sup> While these earlier studies have suggested that “the last gasp” provides both



**Figure 3** A representative tracing of the morphology of gasping and associated changes in aortic pressure (AoP) and intracranial pressure (ICP) during ventricular fibrillation (VF).



increased circulation and ventilation, the present study demonstrated that the gasping reflex may also result in an immediate decrease in ICP and rise in cerebral perfusion pressures. As such, this primitive reflex represents an extraordinary brainstem capacity to preserve vital organ function in the setting of a cardiac arrest.

In addition, the results demonstrate a significant albeit weak correlation between depth of gasping and resulting cerebral perfusion. This has significant implications for understanding the possible mechanisms underlying increased survival in animal models of cardiac arrest<sup>4,5</sup> and in observational studies of humans<sup>7–10</sup> wherein the presence of gasping was associated with a favorable outcome. From a teleological standpoint, the gasping reflex appears to optimize cardiopulmonary and thoraco-cranial interactions: the decrease in intrathoracic pressure associated with the primitive brainstem reflex is associated with increase in respiratory gas exchange, increased venous return to the heart, and thus increased cardiac output and increased cerebral perfusion pressure. In this regard, it may be part of the more recently recognized normal physiology associated with breathing in general, wherein decreases in intrathoracic pressure are associated with much more than simple gas exchange.<sup>15–18</sup>

Previous studies in animal models of hemorrhagic shock have shown that a gasp can be generated by phrenic nerve stimulation. When this is combined with an impedance threshold device, ventricular preload and cardiac output has been shown to increase profoundly with improved survival and neurological outcome.<sup>19</sup> The use of such a device during resuscitation might enhance the increase in cerebral perfusion associated with gasping from cardiac arrest resulting in marked improvement in survival and neurological outcome.<sup>20</sup>

We recognize several limitations in our study, including lack of data on survival and electroencephalographic correlates. Additionally, we did not measure cerebral blood flow directly. Finally, we cannot discount the possibility of gasping being an epiphenomenon that might reflect improved perfusion of medullary respiratory centers during untreated cardiac arrest. However, the weight of evidence from several studies suggests that gasping is an important evolutionary mechanism that might aid in reanimation following cardiac arrest.

## Conclusions

Spontaneous gasping is predictable, common and sustained during cardiac arrest and significantly

decreased intra-cranial pressure and increased cerebral perfusion. The resultant pulsatile cerebral perfusion associated with each gasp may help explain improved cardiac arrest survival. A better understanding of the role and control of the gasping reflex may lead to new ways to improve survival rates after cardiac arrest. Based upon this mechanism of gasping, we speculate that devices that enhance the beneficial effect of gasping on intracranial pressure and cerebral perfusion warrant further investigation.

## Conflict of interest statement

Vijay Srinivasan, MD: none; Vinay M. Nadkarni, MD: none; Demetris Yannopoulos, MD: none; Bradley S. Marino, MD, MPP, MSCE: none; Gardar Sigurdsson, MD: none; Scott H. McKnite, BS: none; Maureen Zook, BA: none; David G. Benditt, MD: member of the Board of Directors of Advanced Circulatory Systems Incorporated (ACSI); Keith G. Lurie, MD: co-inventor of the active compression decompression and the impedance threshold devices and founded Advanced Circulatory Systems Incorporated (ACSI) to develop this technology.

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