**Experimental Physiology – *Review Article***

# Breath-holding and its breakpoint

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**This article reviews the basic properties of breath-holding in humans and the possible causes of the breath at breakpoint. The simplest objective measure of breath-holding is its duration, but even this is highly variable. Breath-holding is a voluntary act, but normal subjects appear unable to breath-hold to unconsciousness. A powerful involuntary mechanism normally overrides voluntary breath-holding and causes the breath that defines the breakpoint. The occurrence of the breakpoint breath does not appear to be caused solely by a mechanism involving lung or chest shrinkage, partial pressures of blood gases or the carotid arterial chemoreceptors. This is despite the well-known properties of breath-hold duration being prolonged by large lung inflations, hyperoxia and hypocapnia and being shortened by the converse manoeuvres and by increased metabolic rate.**

**Breath-holding has, however, two much less well-known but important properties. First, the central respiratory rhythm appears to continue throughout breath-holding. Humans cannot therefore stop their central respiratory rhythm voluntarily. Instead, they merely suppress expression of their central respiratory rhythm and voluntarily 'hold' the chest at a chosen volume, possibly assisted by some tonic diaphragm activity. Second, breath-hold duration is prolonged by bilateral paralysis of the phrenic or vagus nerves. Possibly the contribution to the breakpoint from stimulation of diaphragm muscle chemoreceptors is greater than has previously been considered. At present there is no simple explanation for the breakpoint that encompasses all these properties.**

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'We can't do, so we must think'[1]

## Introduction

The precise mechanisms explaining breath-holding and causing the breath at breakpoint are unknown. There are several useful reviews (Mithoefer, 1965; Godfrey & Campbell, 1968, 1969; Porter, 1970; Campbell & Guz, 1981; Lin, 1982; Nunn, 1987). Breath-holding is an unstable state with changes occurring in many interrelated variables. Although for clarity it is simplest to consider each important variable separately, the variables may well interact in ways that we cannot yet investigate by experiment.

This review will be restricted to experiments on humans while voluntarily breath-holding out of water. As yet there is almost no comparable research on animals, because of the difficulty in persuading them to prolong the respiratory cycle even for more than ∼5 s (Orem & Netick, 1986; Orem, 1989). Breath-hold diving (Lin, 1982) will not be considered, because face immersion evokes a diving reflex with different properties (Lin, 1982; Sterba & Lundgren, 1985; Butler & Woakes, 1987). Neither 'involuntary' breath-holding (e.g. central apnoea or suffocation) nor the sensation of breathlessness/air hunger/dyspnoea (Banzett *et al.* 1990; Ward *et al.* 2001) are considered because their precise relationships to the breakpoint are unclear.

There are many gaps in our understanding of breath-holding that raise difficulties in explaining the breakpoint.

The first difficulty is in how to best quantify breath-holding when the underlying control mechanisms are not known. Should measurement be related to potential sensory stimuli (of proprio- or chemoreceptors?), or to some subjective discomfort scale (which still begs the question of what stimulus causes the discomfort)? Without

[1]Anonymous? paraphrased, *attr.* Lord Ernest Rutherford by Jones (1962).

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a definitive answer, breath-hold duration (the time from the start of the breath-hold to the breakpoint breath) is easiest to quantify objectively.

The second difficulty is that even under similar experimental conditions, breath-holds produce discomfort which is not equally tolerated by all subjects. Hence breath-hold duration is variable, between studies, between subjects and within subjects (Fig. 1). Even within the same subject breath-hold duration can be increased by 13–19% with distractions [either by motor tasks (Fig. 2) or by mental arithmetic (Alpher *et al.* 1986)] or by 37% with successive trials (Fig. 3). This occurs even if inflation volume is the same for every breath and atelectasis is prevented by preceding each breath with a maximum lung inflation (Heath & Irwin, 1968). Experimental data on breath-hold duration should therefore be cited with some measure of variability (here, ± s.e.m) and the effect of successive trials, distraction and motivation should always be considered. How can we ever be sure that all subjects are trying equally hard?

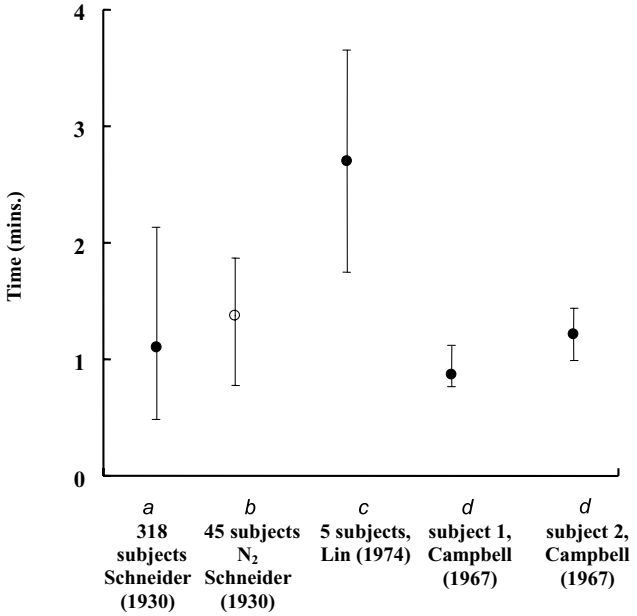


**Figure 1. Variability in mean breath-hold duration between subjects, between studies and within subjects, or mean time to impending unconsciousness while breathing $N_2$**
*a*, mean and range of breath-hold durations of 318 subjects in air at maximum inspiration (Schneider, 1930), used with permission of the American Physiological Society. *b*, mean and range of time breathing $N_2$ from eupnoea until impending unconsciousness of 45 subjects (Schneider, 1930), used with permission of the American Physiological Society. *c*, mean ± 2S.D. breath-hold duration of 5 subjects in air at maximum inflation, used with permission of Lin *et al.* (1974) and the American Physiological Society. *d*, mean and range breath-hold duration of 2 subjects at functional residual capacity in 63% oxygen (Campbell *et al.* 1967), reproduced with permission from *Clinical Science* 1967, **32**, 425–432; © the Biochemical Society and the Medical Research Society.

The third difficulty, causing considerable confusion when comparing different studies, is that breath-hold duration depends on the experimental conditions (e.g. starting lung volume and inspired gas composition). These too must be cited.

Fourth, since many of the important studies used remarkably few subjects (not all of whom were naïve about physiology), or are unconfirmed or may be unrepeatable, it can be difficult to decide which are the most representative experiments.

Fifth, it is still not clear what happens to the respiratory musculature during breath-holding. Expiration in eupnoea is essentially a passive recoil process. Breath-holding is distinct from this because at large inflation volumes there may be some contribution from the voluntary muscles to hold the chest open at a chosen volume against this recoil. Holding cannot be explained simply by closure of the glottis and airway, because it is easy to continue the breath-hold with these structures open (Godfrey *et al.* 1969). The precise activity of the diaphragm, intercostal and accessory muscles during breath-holding has not been definitively established, but the diaphragm may contribute as the 'holding' muscle (see section entitled Paralysis of the diaphragm).

Sixth, although the simplest clue to the breakpoint mechanism should emerge from identifying any manoeuvre enabling breath-holding to unconsciousness, scientific reports of breath-holding to unconsciousness are rare and inconsistent, despite popular mythology. Schneider (1930) stated that 'it is practically impossible for a man at sea level to voluntarily hold his breath until he

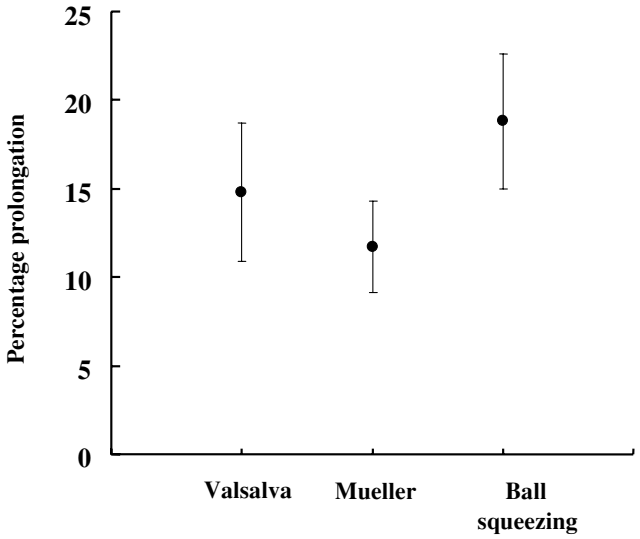


**Figure 2. Percentage prolongation of mean breath-hold duration by various distractions**
Prolongation by Valsalva, Mueller or ball squeezing manoeuvres in air at end expiratory volume (eupnoea), ± s.e.m. in 6 subjects used with the permission of Bartlett (1977) and the American Physiological Society.

becomes unconscious', and subsequent scientific literature supports this in adults. [Anecdotal descriptions of losing consciousness describe subjects breath-holding at low barometric pressures, with low oxygen mixtures or with severe voluntary hyperventilation (Hill & Flacke, 1908; Schneider, 1930; Paulev, 1969). It may also be possible to cause unconsciousness by performing a Valsalva manoeuvre during breath-holding, although not reported by Bartlett (1977).] Even after the longest breath-holds from hyperoxia and hypocapnia, adult subjects break in an apparently involuntary manner and before any obvious impairment of cognitive function (Cooper *et al.* 2003), nor is any intellectual impairment obvious immediately afterwards. It follows from this that it is easiest to view the breath-hold as voluntary and the net stimulus that causes the breakpoint breath (generally an expiration followed by an inspiration) as usually involuntary, i.e. a powerful involuntary mechanism usually overrides the voluntary act of breath-holding. The breakpoint breath may be involuntary even when choosing to stop the breath-hold quite early, or when the breakpoint breath is only an attempt against a still closed airway. Viewing these in this way avoids a number of semantic difficulties, despite our lack of understanding of two crucial points: (a) the extent to which any breath is voluntary or involuntary (Shea, 1996); and (b) where the voluntary command to breath-hold intervenes in the pathway between the central respiratory rhythm generated in the brainstem (Feldman, 1986) and the spinal motoneurones of the respiratory muscles (Mitchell & Berger, 1975).

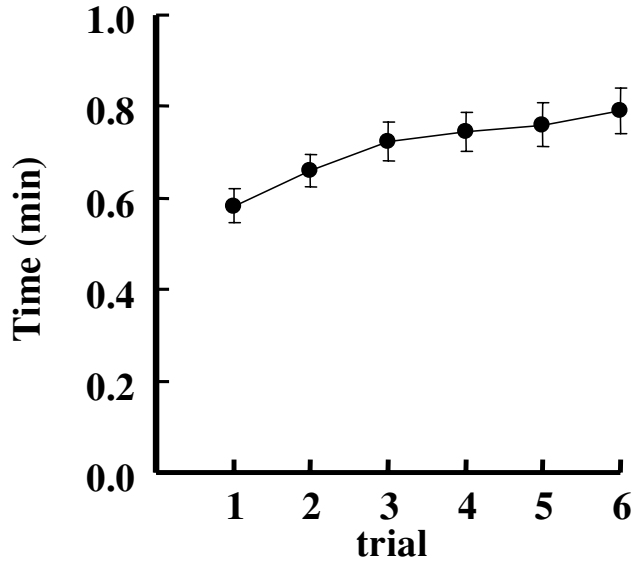


**Figure 3. Prolongation of mean breath-hold duration by successive trials**
Six subjects in 6 successive trials in air at end expiratory volume (eupnoea), ± s.e.m used with the permission of Bartlett (1977) and the American Physiological Society.

Although the breakpoint breath is usually involuntary, some individuals claim to suppress it successfully. Even if they can, it would not appear to be a useful skill to acquire, since suppressing the breakpoint breath must ultimately lead to unconsciousness.

In the absence of manoeuvres that enable consistent breath-holding to unconsciousness, the next useful approach is to identify manoeuvres that prolong breath-hold duration. Since the cited breath-hold durations are so variable, perhaps a sensible guide is to consider manoeuvres important only if they almost double mean breath-hold duration.

### Chest volume shrinkage and metabolic rate

The general effects on breath-hold duration of increasing lung inflation, inspired gas composition and metabolic rate are well known.

Breath-hold duration is increased by increasing lung inflation (Fig. 4*a*). It might be expected that lung volume stays constant throughout breath-holding when the extraction of $O_2$ from the alveoli is counteracted by equal production of $CO_2$ (i.e. presuming a respiratory exchange ratio of 1). In fact, as first shown by a decrease in buoyancy during breath-holding, the lungs gradually contract by 200–500 ml min$^{-1}$ during breath-holding (Stevens *et al.*

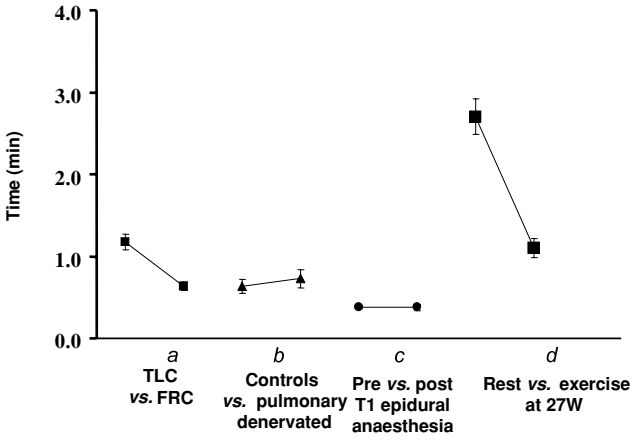


**Figure 4. Effects of lung volume or exercise and lack of effect of pulmonary denervation or spinal anaesthesia on mean breath-hold duration**
The lines indicate points to be compared and the error bars represent S.E.M. *a*, 10 normal subjects in air at total lung capacity (TLC) *versus* functional residual capacity (FRC), reprinted with permission from Flume *et al.* (1996) and from Elsevier. *b*, 5 control subjects *versus* 5 heart lung transplant patients in air at end expiratory volume, used with permission from Harty *et al.* (1996) and Blackwell Publishing. *c*, 4 subjects pre- *versus* post-T1 epidural anaesthesia in air at FRC, reproduced with permission from Eisele *et al.* (1968) and Noble *et al.* (1970), the Novartis Foundation and *Clinical Science* **35**, 23–33, © the Biochemical Society and the Medical Research Society. *d*, 5 subjects in air at maximum inflation, at rest *versus* during bicycle ergometry at 27 W, used with permission of Lin *et al.* (1974) and the American Physiological Society.

1946; Hong *et al.* 1971). This is because failure to remove $CO_2$ from the alveoli abolishes the partial pressure gradient that drives $CO_2$ from blood into alveolar gas, hence the extracted $O_2$ is not replaced by an equal volume of $CO_2$.

Since breath-hold duration depends on initial lung volume, which gradually decreases, one possible mechanism for the breakpoint might be the attainment of some minimum lung (or chest) volume causing sufficient sensory feedback to initiate a breath. (The precise afferents have never been specified since shrinkage classically unloads pulmonary stretch receptors.) Three types of experiment suggest that such a mechanism is not likely.

First, the breakpoint cannot be a simple function of lung shrinkage, because Godfrey *et al.* (1969) found that breath-hold duration was not shortened either if three subjects slowly exhaled during breath-holds or if the rate of lung shrinkage was increased by breath-holding at low ambient pressures.

Second, such a mechanism predicts that removing pulmonary afferents ought to influence breath-hold duration, if not to prolong it indefinitely. Neither is the case. Harty *et al.* (1996) showed that breath-hold duration was no different from control subjects in patients with pulmonary branches of the vagus nerve cut bilaterally following heart and lung transplantation (Fig. 4*b*), and Flume *et al.* (1996) found similar results.

Third, while pulmonary denervation alone does not eliminate all possible chest afferents, most of the remaining afferents ought to be eliminated by spinal anaesthesia. Eisele *et al.* (1968; Fig. 4*c*) found no effect on breath-hold duration of T1 epidural anaesthesia. This is the best evidence that afferents from the intercostal and from most of the accessory muscles of inspiration do not normally make an important contribution to breath-hold duration (unlike diaphragm afferents; see section entitled Paralysis of the diaphragm).

Increasing metabolic rate also shortens breath-hold duration (Rodbard, 1947; Cummings, 1962; Lin *et al.* 1974; Ward *et al.* 2001). Figure 4*d* shows that exercise (bicycle ergometry to at least double metabolic rate) more than halved breath-hold duration. Presumably, decreasing metabolic rate (e.g. by cooling or curarization) should prolong breath-hold duration.

## Oxygen and carbon dioxide

During breath-holding, the arterial or end tidal partial pressure of oxygen $P_{a/etO_2}$ falls below its normal level of ~100 mmHg and that of carbon dioxide $P_{a/etCO_2}$ rises above its normal level of ~40 mmHg. At breakpoint from maximum inflation in air, the $P_{etO_2}$ is typically $62 \pm 4$ mmHg and the $P_{etCO_2}$ is typically $54 \pm 2$ mmHg ($n = 5$; Lin *et al.* 1974), and the longer the breath-hold the more they change. It is remarkable that adults normally cannot breath-hold consistently to unconsciousness, even under laboratory supervision. Nunn (1987) estimates that consciousness in normal adults is lost at $P_{aO_2}$ levels below ~27 mmHg and $P_{aCO_2}$ levels between 90 and 120 mmHg. Breakpoint levels close to these have been reported, e.g. $P_{etO_2}$ levels as low as 24 mmHg, $P_{etCO_2}$ levels as high as 91 mmHg and breath-hold durations of 14 min or more (Schneider, 1930; Ferris *et al.* 1946; Klocke & Rahn, 1959). For comparison, Schneider (1924, 1930) extraordinarily describes surreptitiously switching subjects' breathing to inspire from a spirometer of $N_2$ (and to exhale to room air) and measuring (Fig. 1*b*) the range of breathing times to impending unconsciousness (cyanosis, mask-like facial expression, pupil dilation, eye convergence, falling systolic pressure; Schneider & Truesdell, 1923). This range is similar to his range of breath-hold durations (Fig. 1*a*), yet such symptoms are not characteristic of the breakpoint of breath-holding.

One obvious hypothesis to explain the breakpoint is that once $P_{aO_2}$ falls below or $P_{aCO_2}$ rises above a certain threshold partial pressure, or rate of change of partial pressure reaches a threshold, then chemoreceptor stimulation causes an involuntary breath. The presumption has always been that these would be carotid chemoreceptors [aortic chemoreceptors have no demonstrable effect on breathing in humans (Lugliani *et al.* 1971; Wasserman *et al.* 1975)]. As the following paragraphs show, this 'arterial chemoreceptor hypothesis' is supported by the pronounced effects on breath-hold duration of altering the composition of the inspired gas. It is, however, confounded by the lack of a consistent pattern of arterial gas pressures at breakpoint, by denervation of carotid chemoreceptors failing to prolong breath-holds until unconsciousness and by the ability to breath-hold repeatedly after inspiring asphyxiating gas mixtures.

Breath-hold duration is almost doubled by breath-holding with hyperoxic gas mixtures (Fig. 5*c*), or by preceding breath-holding by voluntary or mechanical hyperventilation to lower $P_{aCO_2}$ levels (Fig. 5*a*). Incidentally, preoxygenation has many practical advantages in studying breath-holding. Not only does it prolong duration, it also results in heart rate barely changing throughout the breath-hold (Gross *et al.* 1976) and in breakpoints that do not occur at $P_{CO_2}$ levels low enough to threaten the brain. [Strictly, there is a risk of atelectasis with breath-holds when the lungs contain 100% $O_2$ (Campbell *et al.* 1967), so some dilution with nitrogen is preferable.]

Alternatively, breath-hold duration is almost halved by breath-holding from hypoxia (Fig. 5*c*), or from hypercapnia, e.g. raising the inspired $P_{CO_2}$ to 65 mmHg (Godfrey & Campbell, 1969; Kelman & Wann, 1971).

The arterial chemoreceptor hypothesis, however, is not supported by the known blood gas pressures at breakpoint. Thus, preoxygenation does not prolong breath-hold duration until mean $P_{aO_2}$ falls to *ca.* 62 mmHg.

Instead, the breakpoint occurs while $P_{etO_2}$ is still remarkably elevated, e.g. 553 ± 16 mmHg, $n = 5$ (Lin *et al.* 1974). Conversely, hypoxia does not shorten breath-hold duration until $P_{aO_2}$ falls to 62 mmHg. Instead the breakpoint occurs at the even lower $P_{aO_2}$ values of 24–43 mmHg (Ferris *et al.* 1946). Similarly, hypercapnia does not shorten breath-hold duration until $P_{etCO_2}$ rises to 54 mmHg (Kelman & Wann, 1971) and $P_{etCO_2}$ can reach 70 mmHg (Godfrey & Campbell, 1969). Furthermore, the breakpoint of breath-holds from hypocapnia occurs at $P_{etCO_2}$ levels between 48 ± 3 (Cooper *et al.* 2003) and 71 ± 3 mmHg (Klocke & Rahn, 1959). Nor is the breakpoint at some unique combination of low $P_{etO_2}$ and high $P_{etCO_2}$ (Klocke & Rahn, 1959). Indeed, even after the longest possible breath-holds from hypocapnia with preoxygenation, blood gas levels at breakpoint are remarkably benign.

In humans, the carotid bodies provide the only known means of detecting arterial hypoxia (Lugliani *et al.* 1971; Wasserman *et al.* 1975) and of rapidly detecting arterial hypercapnia. The arterial chemoreceptor hypothesis is further opposed by the fact that a breakpoint still occurs following carotid chemodenervation (resection), i.e. denervation does not prolong breath-holding until unconsciousness. Davidson and coworkers (Davidson *et al.* 1974; Gross *et al.* 1976) compared breath-hold duration at inspiratory capacity in five patients following bilateral carotid body resection with that of normal subjects (Fig. 5*b*). Mean breath-hold duration in 100% $O_2$ was almost no different and there were no functionally important differences at breakpoint in their mean $P_{etO_2}$ levels [362 ± 20 *versus* 425 ± 12 mmHg (mean ± S.E.M.) in controls], nor in mean $P_{etCO_2}$ levels [59 ± 2 *versus* 56 ± 4 mmHg(mean ± S.E.M.)]. There can, however, be some ambiguity in interpreting these breath-hold duration data, because they can also be used to show that carotid body denervation does produce a small increase in breath-hold duration, confirmed by (Honda *et al.* 1988). Figure 5*b* shows that mean breath-hold duration in denervated patients in 21% $O_2$ is 54% longer ($P < 0.05$) than in intact subjects and that in 12% $O_2$ it is 65% longer ($P < 0.05$). Nevertheless, if the carotid chemoreceptors are the only means of detecting hypoxia, what mechanism explains how hypoxia continues to shorten breath-hold duration in denervated patients? Possibly, this shortening still occurs because the important action of hypoxia is

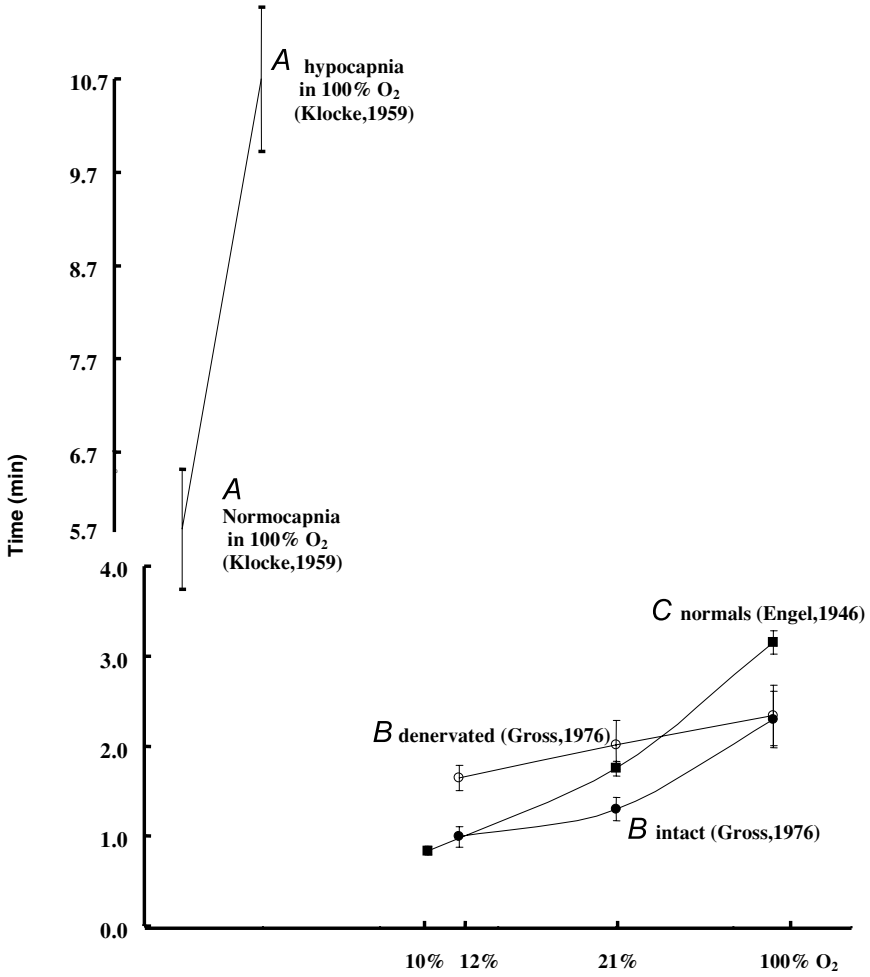


**Figure 5. Effects of oxygenation or hypocapnia and of carotid denervation on mean breath-hold duration**
Lines indicate the appropriate comparisons and the error bars represent S.E.M. *a*, 7 subjects breath-holding at maximal inspiration during normocapnia (41 ± 1 mmHg) or hypocapnia (24 ± 1 mmHg) in 100% $O_2$ (Klocke & Rahn, 1959), used with permission of the American Physiological Society. *b*, 7 intact *versus* 5 denervated subjects in 100, 21 and 12% $O_2$ at inspiratory capacity, used with permission from Davidson *et al.* (1974) and Gross *et al.* (1976), the American Physiological Society and the *New England Journal of Medicine*. *c*, 23 normal subjects breath-holding in 100, 21 and 10% $O_2$ at maximum inflation (Engel *et al.* 1946), reproduced with permission from *Journal of Clinical Investigation*.

not on carotid chemoreceptors but is on diaphragm muscle chemoreceptors (Road, 1990; Jammes & Speck, 1995), whose stimulation may instead make an important contribution to the breakpoint (see section entitled Paralysis of the diaphragm).

Do central chemoreceptors mediate the breakpoint? Their role during breath-holding is still unclear. In as much as $PaCO_2$ reflects their level of stimulation during breath-holding, the lack of a consistent $PaCO_2$ level at breakpoint suggests not. Yet the facts that breath-hold duration in 5 patients with apparently no functional peripheral or central chemoreceptivity (congenital central hypoventilation syndrome- Shea *et al.*, 1993) is almost double that of 5 age and gender matched controls, and that 4/5 had to be told to break by the experimenters, suggests otherwise.

## Repeatedly breath-holding following inspiration of asphyxiating gas

The most dramatic demonstration that breath-hold duration is not simply dependent on blood gas pressures comes from measuring the effect at breakpoint of breathing asphyxiating gas mixtures (i.e. mixtures whose inspiration lowers $P_{aO_2}$ and raises $P_{aCO_2}$ even further) on the ability to make successive breath-holds. This appears to be not widely known, yet was clearly described 51 years ago by Fowler (1954) and is alluded to much earlier (Hill & Flacke, 1908).

If there exists some threshold partial pressure(s) that invokes the involuntary termination of breath-holding, subjects should not be able to make a second breath-hold without first restoring blood gas pressures to normal. Fowler (1954), however, showed that at breakpoint (mean end-tidal $P_{etCO_2}$ 47 mmHg, $n = 3$ and mean oxygen saturation ($S_{aO_2}$ −3% of control values), allowing eight subjects eight breaths of an asphyxiating mixture (8% $O_2$ and 7.5% $CO_2$) enabled them immediately to perform another breath-hold for 20 s. At the breakpoint of the second breath-hold (mean $P_{etCO_2}$ 51 mmHg, $n = 3$ and mean $S_{aO_2}$ −10% of control values), another eight breaths of the asphyxiating gas enabled a further 20 s breath-hold (with gases at breakpoint being a mean $P_{etCO_2}$ of 52 mmHg, $n = 3$ and mean $S_{aO_2}$ of −12%). This was subsequently confirmed with 24 subjects (Flume *et al.* 1994).

Not only is the ability to undertake a second breath-hold essentially independent of blood gas levels, it is also independent of the volume or number of the intervening involuntary breath(s) (Godfrey & Campbell, 1969; Rigg *et al.* 1974; Flume *et al.* 1994, 1995). This ability also persists if performing an isovolume manoeuvre, or merely an inspiratory effort (−12 $cmH_2O$ pressure) against a closed airway (Rigg *et al.* 1974), and even after bilateral lung transplantation in nine subjects (Flume *et al.* 1996). The explanation for this ability may be that stopping the voluntary breath-hold confounds the involuntary breakpoint mechanism, so another breath-hold is always possible. Confounding might be achieved simply as a result of relaxing any tonic diaphragm activity (see section entitled Paralysis of the diaphragm).

## The central respiratory rhythm and breath-holding

The two vital rhythms in all animals are the heart's rhythm and the central respiratory rhythm. Strictly the term 'central respiratory rhythm' is the prerogative of the neurophysiologist, who can record both brainstem respiratory neurone activity and its output in phrenic motoneurones (Feldman, 1986). At present such phrenic recordings are not possible in humans. Nevertheless this term is used here for clarity, even though the closest approximation to its measurement in humans can only be from recording autonomic outflow or skeletal muscle activity.

Humans have almost no voluntary control of their heart beating. For instance, they cannot voluntarily pace their heart rate to a metronome, ∼ or voluntarily change stroke volume, ∼ or voluntarily stop their heart. Humans, however, have much voluntary control of breathing. They can easily pace their breathing rate to a metronome between 1 and 30 breaths $min^{-1}$ and can voluntarily control tidal volume. It has been tacitly presumed that, because breath-holding in humans is voluntary, humans can voluntarily stop their central respiratory rhythm. Evidence has been available since the 1960s, however, showing that this is not the case.

In 1963 Agostoni asked three subjects to swallow catheters so that their tips lay in the oesophagus near the diaphragm, enabling measurement of intrathoracic pressure and indirect measurement of diaphragmatic electromyogram (EMG) activity (Agostoni, 1963). Agostoni showed that during breath-holding no EMG activity was detectable initially. Rhythmic negative pressure fluctuations and simultaneous rhythmic EMG activity appeared towards the end of breath-holding (Fig. 6*A*) and their frequency was within the respiratory frequency range. The amplitude and frequency of these pressure waves increase towards the breakpoint (Lin *et al.* 1974; Whitelaw *et al.* 1981, 1987). Corresponding activity can even be seen in some subjects during breath-holding as rhythmic 'tracheal tugging' against a closed glottis. The simplest explanation is that these are caused by the central respiratory rhythm. This is because the rhythmic EMG and negative pressure waves occur simultaneously, because their frequency and amplitude are within the respiratory range and because they increase as $CO_2$ levels rise towards the end of the breath-hold. This $CO_2$ rise would stimulate the central respiratory rhythm.

The appearance of the respiratory rhythm before the breakpoint shows additionally that the breakpoint itself

is not caused by the sudden restarting of the respiratory rhythm. The failure to record such rhythmic EMG activity throughout breath-holding, however, raises a problem: how to distinguish between the central respiratory rhythm being voluntarily stopped at the start of breath-holding and reappearing towards the breakpoint, or never stopping but merely being undetectable at the start of breath-holding?

Since there is no voluntary control of heart rate, one solution is use respiratory sinus arrhythmia (the decrease in heart period that usually accompanies every breath) to indicate whether the central respiratory rhythm persists during breath-holding. We have recently shown that respiratory sinus arrhythmia in humans is caused predominantly by the central respiratory rhythm, rather than being a secondary effect of rhythmic chest inflation or negative intrathoracic pressure and its mechanical sequelae (Daly, 1986). This is because the central respiratory rhythm and sinus arrhythmia remain during mechanical hyperventilation in normocapnia but are greatly reduced in hypocapnia (Cooper *et al.* 2004). [The phenomenon of post-hyperventilation breathing or

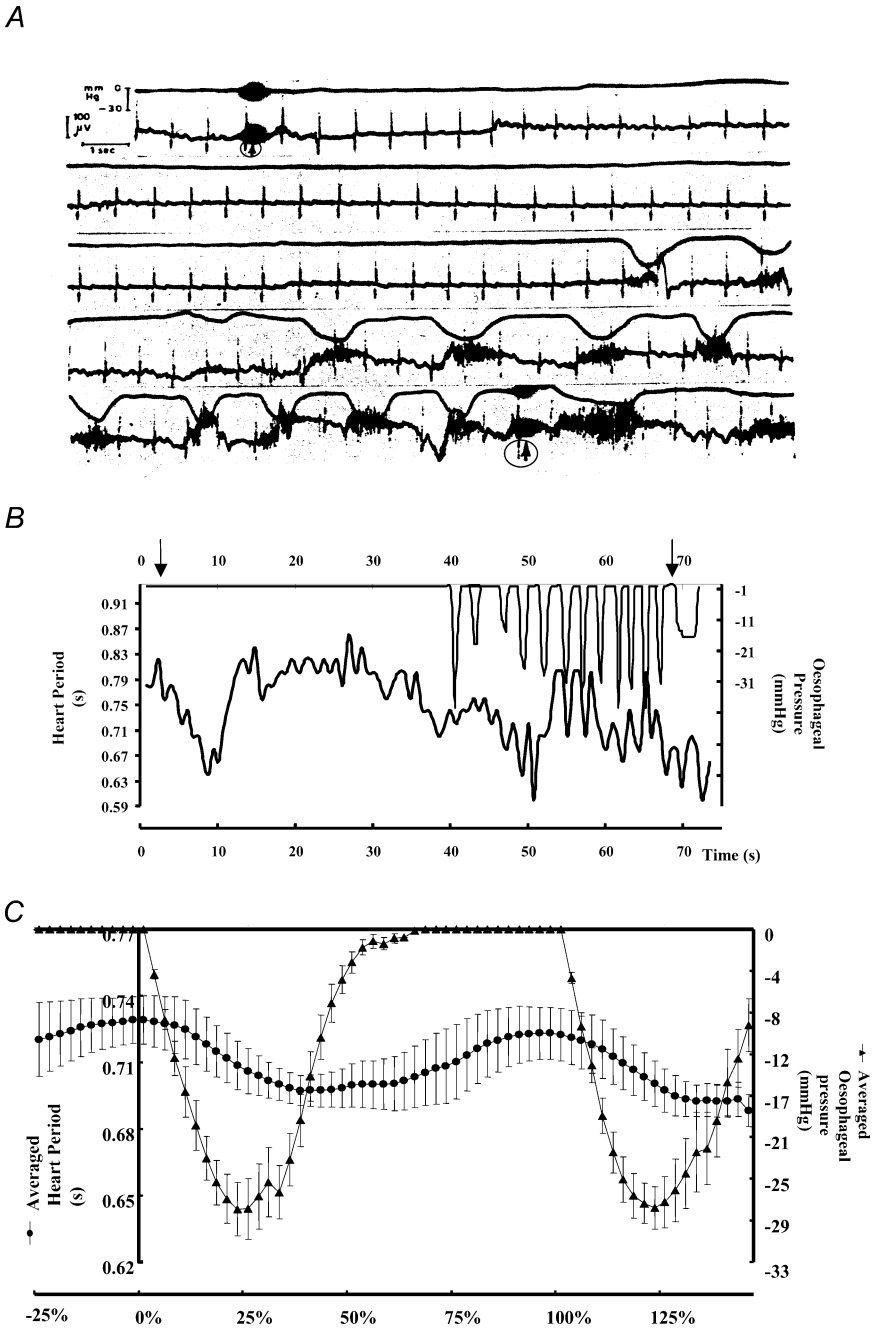


**Figure 6. Diaphragn activity and respiratory sinus arrhythmia during breath-holding**
*A*, appearance of rhythmic diaphragm EMG activity towards the end of breath-holding. Oesophageal pressure (upper trace) and diaphragm EMG activity (lower trace) in one 22-year-old subject during breath-holding at resting lung volume in air, used with the permission of Agostoni (1963) and the American Physiological Society. The start and end of the breath-hold are indicated by circled arrows. *B*, sinus arrhythmia in panel *A* from the start of breath-holding. Using a copy of the original record from panel *A* kindly provided by Professor Agostoni, I have measured the time of each R wave (to within 20 ms) in each ECG artefact to calculate instantaneous heart period as described by Cooper *et al.* (2004) and measured the time and size of each of the 12 oesophageal pressure waves. The start and end of the breath-hold are indicated by arrows. *C*, some of the sinus arrhythmia in panel *A* is respiratory in origin. I have sampled the instantaneous heart period and pressure waves from panel *B* every 2.5% of time between the start of each pressure wave and the next. I then averaged both over the 11 oesophageal pressure wave intervals during the breath-hold as described by Cooper *et al.* (2004). Values plotted are means ± S.E.M. This shows that some of the sinus arrhythmia is respiratory in origin, i.e. some sinus arrhythmia shows a similar relationship to rhythmic diaphragm activity (heart period decreases during inspiration) to that seen during eupnoea (see Fig. 1*C* of Cooper *et al.* 2004).

after-discharge (Tawadrous & Eldridge, 1974) is not detectable in such experiments (Cooper *et al.* 2003, 2004).]

There has been considerable debate over whether sinus arrhythmia persists during breath-holding (Angelone & Coulter, 1965; Davies & Neilson, 1967*a*,*b*; Valentinuzzi & Geddes, 1974; Hirsch & Bishop, 1981; Daly, 1986; Fritsch *et al.* 1991; Eckberg & Sleight, 1992; Pawelczyk & Levine, 1995; Trzebski & Smietanowski, 1996; Passino *et al.* 1997; Piepoli *et al.* 1997; Trzebski *et al.* 2001; Javorka *et al.* 2001). Part of this debate arises because subjects rarely breath-hold in air for longer than 1 min and often for only 20–45 s. This is barely long enough for a few central respiratory cycles to occur, never mind resolving whether or not sinus arrhythmia also persists and reveals them. Prolonging breath-hold times to *ca.* 4 min using preoxygenation is, however, sufficient to test whether sinus arrhythmia is present and whether sinus arrhythmia behaves as if the central respiratory rhythm continues from the start of breath-holding. We have shown in such prolonged breath-holds in 10 subjects that sinus arrhythmia does persist from the start of breath-holding (e.g. Fig. 7*E*) and possesses the $CO_2$ sensitivity characteristic of the central respiratory rhythm (Cooper *et al.* 2003). When preparing this review, Professor Agostoni kindly gave me a copy of his original data (Fig. 6*A*) showing diaphragm activity with a large ECG artefact during breath-holding. Figure 6*B* shows that there is sinus arrhythmia from the start of breath-holding in these data too, and Fig. 6*C* shows that some of this sinus arrhythmia is respiratory in origin. [The sinus arrhythmia (Fig. 6*B*) is not obviously different when these pressure/EMG waves first appear, nor is it generally believed that sinus arrhythmia is suddenly

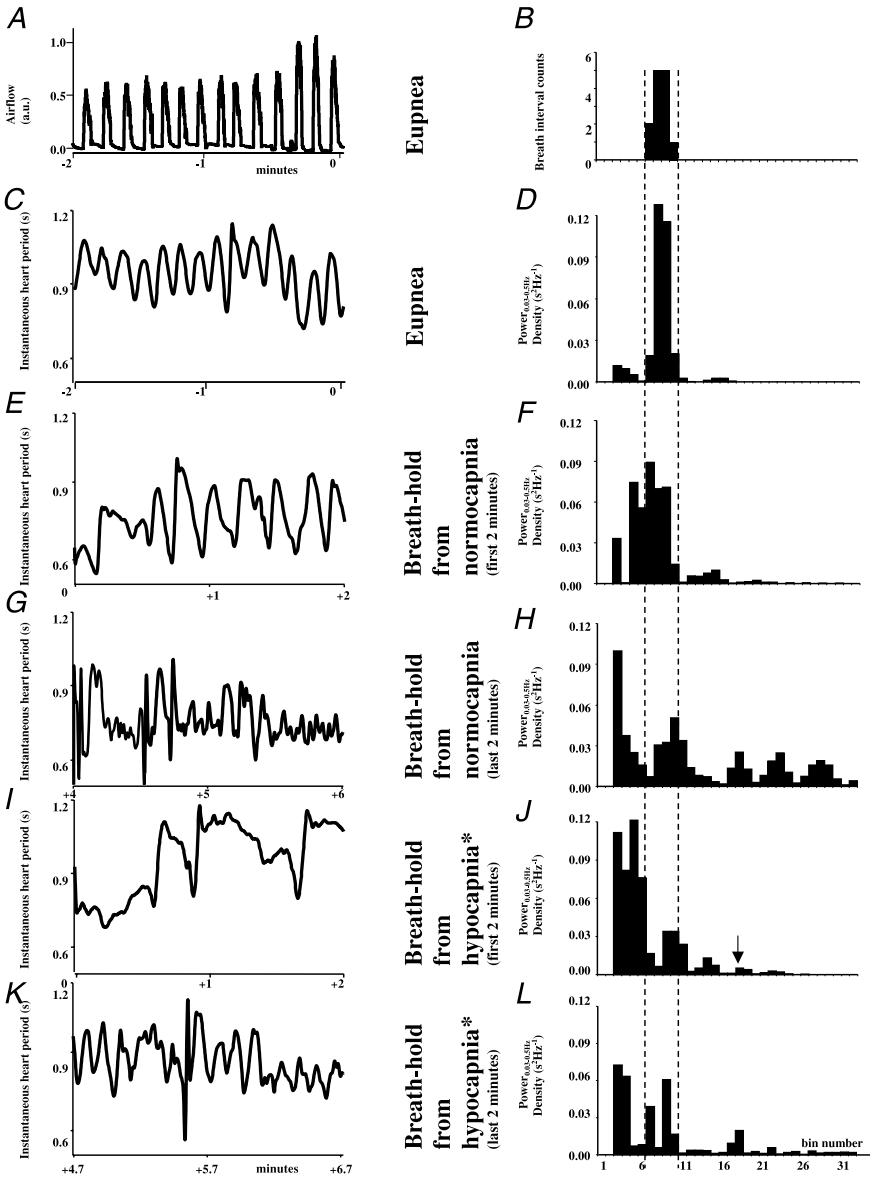


**Figure 7. Sinus arrhythmia in the subject with the longest breath-hold (min) in normocapnia with preoxygenation at maximum inflation (Cooper *et al.* 2003), used with the permission of the American Physiological Society**
*A*, air flow in eupnoea immediately preceding breath-holding. *B*, distribution of the 13 breath intervals in *a* within the 30 usable bins describing frequency (0.03–0.5 Hz). The dashed line indicates his eupneic frequency range (bins 7–10). *C*–*L*, instantaneous heart period and its $power_{0.03–0.5Hz}$ density spectra in eupnoea (*C* and *D*), the first 2 min (*E* and *F*) and last 2 min (*G* and *H*) of breath-holds from normocapnia (6 min. duration) and from hypocapnia (6.7 min duration) (I–L) ['hypocapnia' corrects the typographical error in the original Fig. 1 of (Cooper *et al.* 2003)]. The horizontal scale in *B*, *D*, *F*, *H*, *I* and *J* indicates each of the 32 bins describing 0–0.5 Hz. [The arrow in *J* indicates the lack of evidence for any short-term potentiation or after-discharge (Tawadrous & Eldridge, 1974) following mechanical hyperventilation because there is no increase in $power_{0.03–0.5Hz}$ at the frequency (bin 18) of the preceding ~20 min of mechanical hyperventilation.]

different towards the end of breath-holding (Cooper *et al.* 2003). It is not clear whether the moment these waves first appear, sometimes named the physiological breakpoint (Lin, 1982) as distinct from the conventional breakpoint, has any particular significance.]

In the absence of any more direct measures of the central respiratory rhythm being available in humans, all this evidence indicates that the central respiratory rhythm is present throughout breath-holding.

This conclusion has several important implications.

First, it shows that humans cannot voluntarily stop, i.e. that they do not have absolute control of, their central respiratory rhythm. Instead they breath-hold merely by voluntarily 'holding' the chest and suppressing expression of their central respiratory rhythm. Where and how voluntary suppression occurs remain unclear. Is the location the brainstem but effectively bypassing the respiratory input to cardiac vagal preganglionic neurones, or is it more distal, e.g. in the spinal cord? (Nathan & Sears, 1960; Mitchell & Berger, 1975). Is voluntarily 'holding' assisted by some tonic voluntary contraction of the diaphragm? Does this voluntary input to phrenic motoneurones continue during each expiratory phase of the central respiratory rhythm and override any potential inhibition from a central respiratory drive potential (Sears, 1966)? Such mechanisms, if they do operate in this way, could so easily explain how breath-holding suppresses expression of the central respiratory rhythm, without stopping the rhythm itself.

Second, it has caused confusion previously to describe a breath-hold as inspiratory, because this implies that the central respiratory rhythm has stopped in its inspiratory phase, or for an expiratory breath-hold to have stopped in its expiratory phase. Better terminology would be an inflation or a deflation breath-hold. Or is it only the starting lung volume as held by the diaphragm that is important? Is the means of reaching it irrelevant?

Third, some studies use breath-holding to study physiological mechanisms with the presumption that the central respiratory rhythm has stopped. This presumption appears invalid. Strictly, such studies only consider mechanisms in the absence of rhythmic pulmonary inflation. It may be invalid even for breath-holds from hypocapnia, since the hypocapnia levels safely attainable in humans would not necessarily stop the central respiratory rhythm as measured in animals (Boden *et al.* 1998).

Fourth, might all chemoreceptor contributions to the breakpoint be mediated through the central respiratory rhythm?

## Paralysis of the diaphragm

Between 1967 and 1969 Campbell paralysed voluntary musculature with *d*-tubocurarine in two atropinized subjects (one had an oral airway inserted) and mechanically ventilated them with 63% $O_2$ via a facepiece (Campbell *et al.* 1966, 1967, 1969). Voluntary control of one arm was retained (using an arterial occlusion cuff to restrict the entry of curare) to enable the subject to signal when they wanted to 'breathe'. The ventilator was then switched off and the conscious subjects were asked to signal when they wanted ventilation restarted. Their mean 'breath-hold' durations (Fig. 1*d*) were prolonged at least threefold (Campbell *et al.* 1967), and after ∼4 min the experimenters intervened. $P_{etCO_2}$ levels at 'breakpoint' of up to 72 mmHg were reported (Campbell *et al.* 1969). When they could again talk, subjects reported no distressing symptoms of suffocation or of discomfort.

Interpretation of this remarkable experiment has been challenged in two ways. First, Campbell's results were not confirmed. Gandevia *et al.* (1993) performed a similar experiment (except that in all 3 subjects the trachea was intubated transnasally) and found that curare did not prolong 'breath-hold' duration (mean duration of control breath-holds 79 s, range 48–110 s *versus* curarized 'breath-holds' of 78 s, range 34–120 s) and reported severe dyspnoea at 'breakpoint'. In neither study, however, could the subjects be termed naïve to possible outcomes! Secondly, curare must prolong 'breath-hold' duration to a small extent because it reduces metabolic rate.

Both challenges may be addressed. First, while greatly respecting the enormous courage of Gandevia's subjects in consciously placing their lives in the experimenters' hands, they may have suffered additional discomfort from intubation and their $P_{etCO_2}$ levels at 'breakpoint' [$43 \pm 3$ *versus* $43 \pm 3$ mmHg (means ± S.D.) without paralysis] were almost normal. [The equally remarkable study by Banzett *et al.* (1990), of the perception of air hunger when awake, curarized subjects were mechanically ventilated continuously and $P_{etCO_2}$ was changed in 3–4 mmHg steps, is so unlike the brief and non-steady state of breath-holding that it is not directly comparable. Nevertheless the study by Banzett *et al.* (1990) only eliminates the role of diaphragm/respiratory muscle contraction in air hunger and is still consistent with a possible role of diaphragm chemoreceptors in air hunger].

Secondly, any debate between Campbell's and Gandevia's remarkable, probably irreconcilable and unrepeatable studies can be side-stepped by considering the studies of Noble *et al.* (1970, 1971). They injected local anaesthetic into the phrenic nerves bilaterally, therefore restricting the paralysis to the diaphragm, i.e. without such a life-threatening manoeuvre on conscious subjects and with less effect on metabolic rate. Noble and coworkers achieved similar approximate doubling (Fig. 8*a*) of breath-hold duration in three subjects (but still did not prolong breath-hold duration to unconsciousness). Moreover, 'in all three phrenic block subjects the sensation [of

breath-holding] was decreased or altered'. Similar results were found by Eisele *et al.* (1972).

If Campbell's, Noble's and Eisele's experiments are accepted, the obvious interpretation is that: (a) curarization or phrenic paralysis prolongs breath-hold time by preventing any diaphragm contraction and hence reduce generation of afferent feedback; and (b) it is afferent feedback from the diaphragm that normally causes the feeling of discomfort and may oppose the ability to breath-hold.

This interpretation however, raises several questions.

**(1) What known afferent pathways can explain these effects?.** Diaphragm afferents travelling in the phrenic nerves are one obvious pathway. Although traditional respiratory neurophysiology (Feldman, 1986) does not normally consider that feedback from the diaphragm directly modulates the central respiratory rhythm, there is now substantial evidence that phrenic afferents may modulate diaphragm activity (Road, 1990; Jammes & Speck, 1995). Approximately 30% of the phrenic nerve in cats, dogs and rats carries afferents, i.e. 500–800 afferents per nerve (Ferguson, 1891; Landau *et al.* 1962; Langford & Schmidt, 1983). Some of these are muscle proprioreceptors (Corda *et al.* 1965; Balkowiec *et al.* 1995), but the majority appear to be type III or type IV afferents (Landau *et al.* 1962; Duron & Condamin, 1970; Langford & Schmidt, 1983). Some of these are active during spontaneous breathing, have receptive fields in the diaphragm and are stimulated by chemoreceptor stimulants (e.g. potassium, lactic acid, capsaicin or phenyl diguanide, or asphyxia or fatigue); in turn these stimuli, or electrical stimulation of phrenic afferents, may have reflex excitatory and/or inhibitory effects on the diaphragm (Graham *et al.* 1986; Jammes *et al.* 1986; Supinski *et al.* 1989, 1993; Balkowiec *et al.* 1995; Iscoe & Duffin, 1996). Little is known about the role of diaphragm afferents in humans, although there is indirect evidence that they may be important (Nathan & Sears, 1960; Green *et al.* 1978). Strictly, however, the experiments of Campbell, Noble and Eisele establish only the effects on breath-hold duration of motor paralysis of the diaphragm. Without selective blockade of phrenic afferents only, they do not establish that the afferent pathway is via the phrenic nerves.

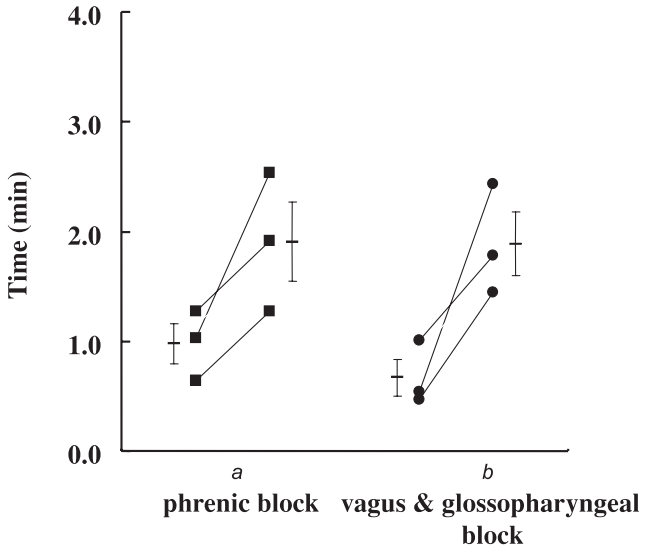


**Figure 8. Prolongation of breath-hold duration mean ± s.e.m by bilateral phrenic block or by bilateral vagus and glossopharyngeal nerve block**
Prolongation of breath-hold duration by bilateral phrenic block (*a*), reproduced with permission from Noble *et al.* (1970, 1971), the Novartis Foundation and *Clinical Science* **41**, 275–283, © the Biochemical Society and the Medical Research Society, or bilateral vagus and glossopharyngeal nerve block (b), reproduced with permission from Noble *et al.* (1970) and the Novartis Foundation (and see also Guz *et al.* 1966; Guz, 1966). Note that breath-holds were at end expiration (FRC). They were from 100% $O_2$ for (*a*) (Noble *et al.* 1971) and apparently mostly from 100% $O_2$ for (*b*) (Guz *et al.* 1966; Guz, 1966; Noble *et al.* 1970). Squares and circles indicate individual subjects with the means ± S.E.M. for each pre- and post-block condition indicated as horizontal bars.

**(2) What does this afferent feedback indicate?.** Does it indicate proprioreceptor activity (the presence of any tonic diaphragmatic contraction, or the absence of rhythmic diaphragm contractions), or merely diaphragm fatigue (i.e. diaphragm chemoreceptor activity; Fisher & White, 2004)? Without knowing the precise status of the respiratory muscles during breath-holding this is unclear. To explain how the chest is held inflated at large volumes during breath-holding, even with an open glottis and airway, it might be presumed that there is some tonic activation of the diaphragm during breath-holding. Yet in humans there is no direct evidence about what breath-holding does to phrenic motoneurone activity. EMG activity is usually recorded only indirectly from what is topologically the body surface during breath-holding (Agostoni, 1963), so it is hardly surprising that only rhythmic diaphragm EMG activity is detected and only towards the end of breath-holding (Fig. 6*A*). The possibility remains that voluntarily 'holding' involves some tonic and almost isometric diaphragm contraction ('almost' because of lung shrinkage throughout breath-holding). Such a mild contraction may not always be discernable as a diaphragm EMG signal detected on the body surface. Could such an unusual isometric contraction induce diaphragm fatigue sufficient to stimulate diaphragm muscle chemoreceptor afferents which contribute to the breakpoint. Even if the diaphragm does not contract tonically during breath-holding, some stimulation of diaphragm chemoreceptors is an intriguing alternative to the old arterial chemoreceptor hypothesis and may make more sense of many disparate observations. It could explain the effects of blood gas levels on breath-hold duration, if such muscle chemoreceptor activity

is increased by arterial hypoxia and hypercapnia and decreased by hyperoxia and hypocapnia. It could also explain how stopping a voluntary breath-hold confounds the involuntary breakpoint mechanism, if stopping reduces stimulation of both muscle chemoreceptors (by restoring muscle blood flow) and proprioreceptors.

**(3) How is this feedback perceived?.** Normally humans have almost no sense of diaphragm *per se,* so precisely what is perceived from diaphragm muscle afferents during breath-holding is unclear. Even if the muscle afferent signal is only perceived vaguely as discomfort, the ability to tolerate such discomfort could explain the notorious variations in breath-hold duration (cf. the variation in holding times for isometric contractions in other voluntary muscles).

**(4) Where are its principal integration sites?.** The facts that the central respiratory rhythm continues during breath-holding and that the breakpoint breath is usually involuntary suggest that the involuntary respiratory rhythm in the brainstem is the obvious principal site for integration. It is also possible, however, that this diaphragm feedback is important in opposing voluntary control of breathing and may act cortically or at a spinal level (Nathan & Sears, 1960). There is evidence for something similar to such feedback reaching consciousness in humans. This is the fact that when awake and mechanically hyperventilated in hypocapnia, volunteers almost never stop breathing (apnoeas $\leq 12$ s) when the ventilator is switched off (Shea, 1996; Cooper *et al.* 2004). Yet when asleep, switching off in hypocapnia always produces apnoea $\geq 79$ s (Henke *et al.* 1988; Datta *et al.* 1991).

### Anaesthetic blockade of the vagus nerves

Guz, Noble and coworkers injected lignocaine bilaterally into the vagus (X) and glossopharyngeal (IX) nerves of three normal volunteers to block all afferent sensory traffic (Guz, 1966; Guz *et al.* 1966; Noble *et al.* 1970). They showed (Fig. 8*b*) that this alleviated the distress of breath-holding and, while not prolonging breath-hold duration indefinitely, still approximately trebled their mean breath-hold duration. (N.B. Fig. 8*b* breath-holds apparently were mostly from 100% $O_2$ and they appear short only because they were started from end expiration, whereas those in Fig. 5*b* were from inspiratory capacity.) Noble *et al.* (1970) made a further and ingenious connection:

> 'The sensation of breath-holding was alleviated by vagal block, phrenic block, transection at the 3rd cervical segment and poliomyelitis. The sensation arises from frustrated contractions of the diaphragm stimulated by a reflex with its afferent limb in the vagus.'

This study has been neglected because such anaesthesia also blocks the afferents (Davidson *et al.* 1974) from the carotid (IX) and aortic (X) chemoreceptors and from the lungs (X). But we now know that there appears to be no aortic chemoreceptor contribution to breathing in humans, that the arterial chemoreceptor contribution to breath-hold duration is negligible in 100% $O_2$ (Fig. 5*b*), and that section of vagal afferents from the lungs has no effect (Fig. 4*b*) on breath-hold duration. The study by Noble and coworkers therefore deserves reconsideration. Their conclusion, 'it thus appears that the build up of the stimulus to diaphragmatic contractions during breath-holding is dependent on vagal afferent information. We would welcome suggestions as to the precise nature of

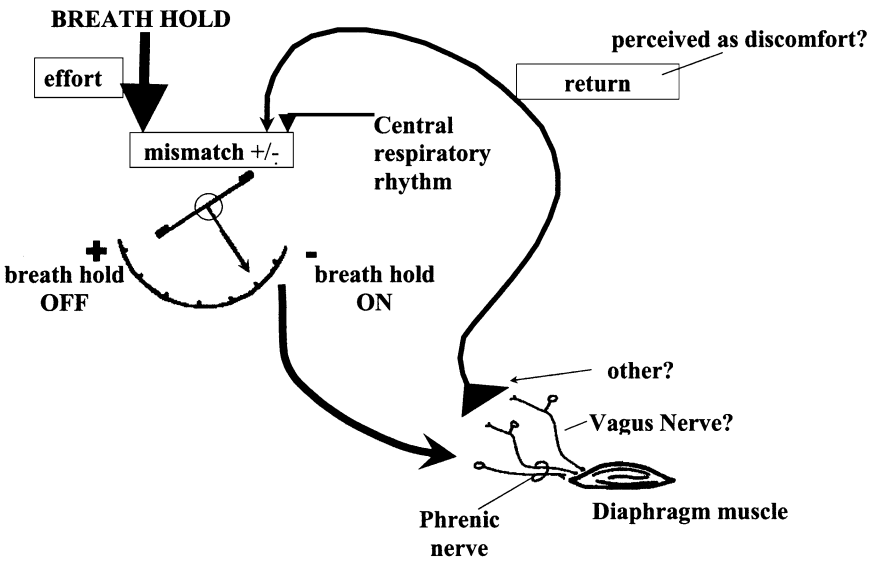


**Figure 9. One possible scheme for breath-holding and its breakpoint**

this afferent mechanism' poses a challenge that no one appears to have taken up. Their experiment is particularly important because, since vagal blockade approximately trebled breath-hold duration while the phrenic afferent pathway was still intact, it implies that [non-pulmonary] vagus nerves may and phrenic nerves may *not* provide the principal afferent pathway from the diaphragm!

### A unifying hypothesis for the breakpoint of breath-holding?

The simplest 'single variable' hypotheses based on either pressure levels of arterial blood gases or lung volume can be ruled out. Strictly, hypotheses based on various combinations of blood gases with lung volume (Mithoefer, 1965) cannot be excluded, but the complexity of multiple variable hypotheses makes them difficult to test scientifically.

Campbell and coworkers (Godfrey & Campbell, 1968, 1970; Rigg *et al.* 1974) consider the breakpoint in terms that can be simplified to a mismatch (inappropriateness) of return for effort (tension/length). These terms have still not been rigorously defined, but experiments since 1970 enable a further attempt (see Fig. 9).

Now that we know the central respiratory rhythm continues during breath-holding (and that the factors that increase it usually promote the breakpoint), defining these terms becomes more complex. The 'return' appears to involve muscle chemo- and proprioreceptor afferent activity from the diaphragm. This may be perceived consciously only as the discomfort that opposes breath-holding. Nevertheless, since neither phrenic nor vagal blockade enables breath-holding to unconsciousness, are we still missing a crucial element of 'return'?

The 'effort' is to perform the unusual act of voluntarily 'holding' the chest (with the a contribution from diaphragm?). It might simply be a corticospinal input to phrenic motoneurones that bypasses the premotor respiratory neurones in the brainstem. In contrast, the breath that identifies the breakpoint is usually involuntary so presumably is not involved in this 'effort'.

We are, however, still no further in understanding what the term 'mismatch' means. Is the mismatch between the size of the effort *versus* return as the combined size of the diaphragm afferent signal with the central respiratory rhythm? Whatever it is, the smaller the mismatch the longer the breath-hold. Conversely, the bigger the mismatch the more likely is the breakpoint. And the breakpoint breath must cause the mismatch to disappear.

Treating mismatch in this way could explain a number of disparate properties of breath-holding, as follows.

First, mismatch is reduced by anything that reduces feedback from diaphragm afferents (e.g. curare, phrenic and possibly vagal block, arterial hyperoxia and hypocapnia) or that reduces the central respiratory rhythm (e.g. arterial hyperoxia or hypocapnia, or increasing lung volume to increase the $O_2$ and $CO_2$ reservoir, or decreasing metabolic rate). These will prolong breath-hold time.

Second, mismatch is increased by anything that increases feedback from diaphragm afferents (e.g. any tonic diaphragm activity and possibly arterial hypoxia and hypercapnia) or that increases the central respiratory rhythm (e.g. arterial hypoxia or hypercapnia, or decreasing lung volume, or increased metabolic rate). These will shorten breath-hold time.

Third, because the breakpoint breath (releasing any tonic diaphragm contraction?) causes mismatch to disappear, another breath-hold is always possible.

Overall, considering a greater role for the diaphragm appears to provide a better explanation for the breakpoint, despite the lack of substantial supporting experimental evidence. This is why the paraphrase of Rutherford may be apt: 'We can't do, so we must think'. Perhaps recent developments in non-invasive imaging will improve our understanding of mismatch, effort and return.

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