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REVIEW ARTICLE

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Physiology of static breath holding in elite apneists

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Abstract

Breath-hold-related activities have been performed for centuries, but only recently, within the last ~30 years, has it emerged as an increasingly popular competitive sport. In apnoea sport, competition relates to underwater distances or simply maximal breath-hold duration, with the current (oxygen-unsupplemented) static breath-hold record at 11 min 35 s. Remarkably, many ultra-elite apneists are able to suppress respiratory urges to the point where consciousness fundamentally limits a breath-hold duration. Here, arterial oxygen saturations as low as ~50% have been reported. In such cases, oxygen conservation to maintain cerebral functioning is critical, where responses ascribed to the mammalian dive reflex, e.g. sympathetically mediated peripheral vasoconstriction and vagally mediated bradycardia, are central. In defence of maintaining global cerebral oxygen delivery during prolonged breath holds, the cerebral blood flow may increase by ~100% from resting values. Interestingly, near the termination of prolonged dry static breath holds, recent studies also indicate that reductions in the cerebral oxidative metabolism can occur, probably attributable to the extreme hypercapnia and irrespective of the hypoxaemia. In this review, we highlight and discuss the recent data on the cardiovascular, metabolic and, particularly, cerebrovascular function in competitive apneists performing maximal static breath holds. The physiological adaptation and maladaptation with regular breath-hold training are also summarized, and future research areas in this unique physiological field are highlighted; particularly, the need to determine the potential long-term health impacts of extreme breath holding.

KEYWORDS

apnoea, breath-holding, diving, free diving

1 | INTRODUCTION

Historical interest in breath holding (apnoea) can be traced back to ancient Greek mythology, as was often recounted by Herodotus, and readily recognized by the ~2000 year tradition of the Ama, who breath-hold dive for shellfish off the cost of Japan and Korea. However, the quest to push human limits of a volitional breath hold is fuelled largely through the recent (past ~30 years) emergence of apnoea as an organized sport. The Association Internationale pour le Développement de l'Apnée (AIDA) and the World Confederation of Underwater Activities (CMAS) are two principal organizing bodies that broadly characterize competitive apnoea into separate disciplines associated with a maximal breath-hold time, or depth and distance swum with a single breath of air. In a broader sense, apnoea-related sport also encompasses spearfishing, underwater photography, underwater hockey and rugby, underwater target shooting and synchronized swimming. Regardless, a central facet of all apnoea-related discipline is the capacity to withstand the severe physiological stressors that arise with prolonged breath holding. The focus of this review is on the pertinent physiology of static (non-exercising) maximal breath holds in elite apneists. Currently, the world record static breath hold in men, performed while lying face down in water, is a remarkable 11 min 35 s.

Excluding the very essential conscious capability to suppress powerful urges to breathe, the basic physiological capacity to perform a prolonged breath hold involves prioritizing oxygen-rich blood flow to the brain and using the available oxygen as efficiently and as little as possible. The Weddell seal (*Leptonychotes weddellii*) is an expert at this, with recorded dive times longer than an hour. Yet this conceptually

New Findings

- **What is the topic of this review?**
  This review provides an up-to-date assessment of the physiology involved with extreme static dry-land breath holding in trained apneists.
- **What advances does it highlight?**
  We specifically highlight the recent findings involved with the cardiovascular, cerebrovascular and metabolic function during a maximal breath hold in elite apneists.

simple process for oxygen conservation in humans involves complex, interacting and, sometimes, paradoxical physiological mechanisms.

In this review, we delineate these mechanisms, with particular emphasis on the novel descriptions of the cardiovascular, cerebrovascular and metabolic perturbations studied within the last 10 years. Focus is placed on studies performed in elite apneists (where breath holds exceed 5 min); however, a large body of the basic concepts is inherently derived from studies in naive (untrained) breath holders, especially related to the basic physiological adjustments of apnoea that are discussed in context with the mammalian dive response and the factors that can influence it. Lastly, the adaptations (and maladaptations) associated with the practice of extreme breath holding are briefly discussed. Importantly, although prolonged breath holding is often performed at depths, the mechanical constraints and physiological changes associated with increased barometric pressure are not discussed here. Moreover, the focus is on static (non-exercising) apnoea. For a review on the physiological perturbations of apnoea with exercise and at depth, see Dujic and Breskovic (2012), Lindholm and Lundgren (2009) and Schagatay (2010, 2011); and for more classical reviews on the basic physiological perturbations of breath holding in humans, see Foster and Sheel (2005), Gooden (1994) and Lin (1982).

2 | THE BREATH-HOLD BREAK POINT IN ELITE APNEISTS

Hypoxia- and hypercapnia-induced chemosensation, removal of inhibitory pulmonary afferent nerve activity (i.e. removal of phasic lung stretch) and mounting nerve activity from the continually active respiratory rhythm generator are each central to the collective respiratory stress of a static breath hold, as previously outlined in *Experimental Physiology* (Parkes, 2006) and by others (Godfrey & Campbell, 1968; Lin, Lally, Moore, & Hong, 1974; Mithoefer, 1965). Inevitably, when a breath hold is extended, these intensifying respiratory signals cause involuntary contractions of the diaphragm and inspiratory muscles, commonly referred to as involuntary breathing movements (IBMs). The initiation of the first IBM is termed the 'physiological break point' (Lin et al., 1974) and is where the motivated but naive apneist will break their breath hold and reinstate breathing. However, in elite apneists the breath-hold breaking point can occur after ~75 intensifying IBMs, well beyond the 'physiological break point'. The major difference between the naive and elite breath hold, in turn, rests on a mental drive for elite apneists to suppress the urge to breathe and maintain a closed glottis and mouth throughout the IBMs. The latter part of the elite apnoea involving IBM suppression is coined the 'struggle phase', *versus* the 'easy going phase'. Figure 1 depicts a typical elite dry static breath hold, where the easy and struggle phase are illustrated through chest wall movements associated with the IBMs.

When elite apneists are motivated and consciously suppress all respiratory sensory information/IBMs, the determining physiological factor of a maximal breath-hold breaking point fundamentally rests upon a critical level of hypoxaemia before loss of consciousness. As a result, inhibiting respiratory sensory information (e.g. carotid body silencing with low-dose dopamine) has no beneficial impact on a maximal breath-hold duration in the most elite apneists (Bain et al., 2015a).

During static dry breath holds in a laboratory setting, partial pressures of arterial oxygen (P_{aO_2}) as low as ~20 mmHg have been reported (Bain et al., 2016a, 2017a; Willie et al., 2015). Figure 2 illustrates a typical arterial blood gas profile throughout a prolonged dry static breath hold. Importantly, the most motivated elite apneists generally break a maximal breath hold slightly before reaching an arterial oxygen saturation of ~50% (Bain et al., 2016a, 2017a; Willie et al., 2015), which is a notable level because it is slightly before the theoretical limit for consciousness in humans (Nunn, 1987). Loss of consciousness, however, is eerily too common in elite apnoea competition. Indeed, the classical view that a breath-hold until unconsciousness is a merely a 'myth' and 'impossible' (Parkes, 2006) has been proved otherwise by the emergence of competitive apnoea. For obvious safety reasons, the major organizing bodies for competitive apnoea (AIDA and CMAS) have implemented strict rules disqualifying any competitor who is not alert upon breaking the breath hold.

2.1 | Elite 'hyperoxic' breath-hold break point

Although extremely dangerous, growing popularity has emerged for breath holds performed with prior 100% oxygen breathing (perhaps stemming from the televised breath hold of 17 min 4 s by the magician David Blaine, in 2008). Under the premise that hypoxaemia (consciousness) fundamentally determines an ultra-elite breath-hold breaking point, it is interesting to comment on the elite breath-hold breaking point with prior 100% O_2 inhalation. In elite apneists, a 'hyperoxic' breath hold may be held for >20 min (Bain et al., 2017b), with the current Guinness world record at 24 min 3 s. At the break point, arterial oxygen tension is well above euoxia (P_{aO_2} of ~350 mmHg; Bain et al., 2017a).

In the untrained apneist, the hyperoxic breath-hold breaking point stems from similar mechanisms to that of a 'normal' breath hold, i.e. from pulmonary afferent nerve activity, the continually active respiratory rhythm generator and (albeit to a lesser extent because of the hyperoxia-induced carotid body attenuation) from chemoreflex

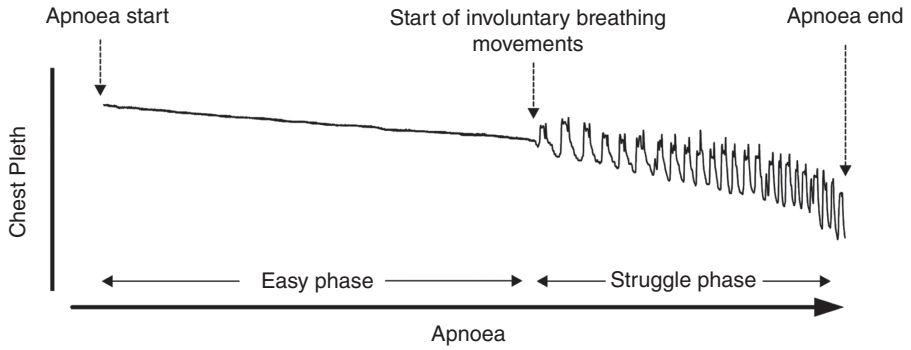

FIGURE 1 Chest wall movements during a 6 min dry static breath hold. The easy-going and struggle phases of an elite breath hold are depicted. The non-elite breath-hold break point occurs before or at the start of involuntary breathing movements. See main text for detail

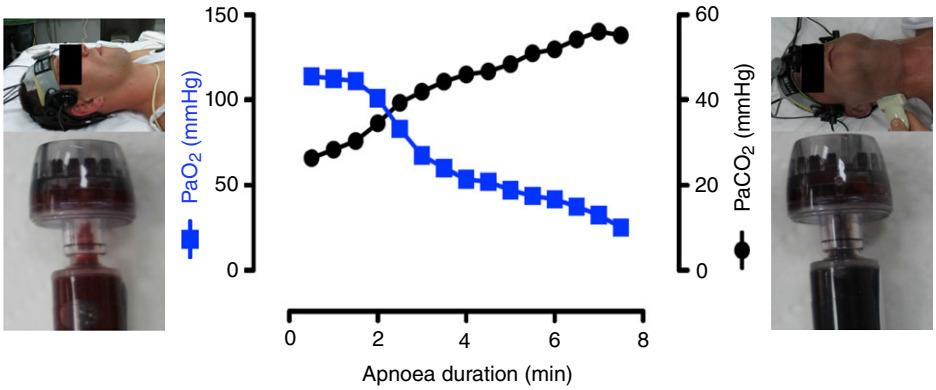

FIGURE 2 Representative illustration of the arterial blood gas profile throughout a maximal dry static breath hold lasting ~8 min. Abbreviations: P_{aCO_2}, partial pressure of arterial carbon dioxide; and P_{aO_2}, partial pressure of arterial oxygen. Left picture: Subject (top) and arterial blood sample (bottom) before commencing the breath hold. Right picture: Subject (top) and arterial blood sample (bottom) at near-break point of the maximal apnoea. Timing of pictured blood samples coincides with subject pictures. Profound cyanosis in the subject's face (right) is evident. Hypoxaemic coloration of the arterial blood sample taken at near-break point (right) is visible by the colour. Data and photographs, with permission, from Willie et al. (2015)

(hypercapnia) stress (Klocke & Rahn, 1959; Parkes, 2006). In contrast, in the elite and motivated apneist, the hyperoxic breath-hold break point is probably explained almost exclusively by severe respiratory muscle discomfort from suppressing up to 100 IBMs and pending lung collapse, which is accentuated with the reduced lung volumes from the disproportionate extraction of oxygen *versus* release of carbon dioxide (Bain et al., 2017b; Hong et al., 1971). The danger of pending lung collapse (atelectasis) is best demonstrated by the fact that ultra-elite apneists terminate a hyperoxic breath hold by inhaling, rather than exhaling. (See Supporting information for video, reproduced with permission, of the current Guinness hyperoxic maximal breath-hold record of 24 min 3 s that demonstrates the inspiratory breath at apnoea break point.) Ultimately, as demonstrated by Klocke and Rahn >50 years ago (Klocke & Rahn, 1959), the theoretical maximal duration of a hyperoxic breath-hold is determined by the length of time before reaching lung residual volume, or atelectasis, which itself is dependent on barometric pressure, vital capacity and consumed oxygen (metabolic rate). The theoretical maximal possible breath-holding time with hyperoxic prebreathing can thus be calculated from the vital capacity divided by the consumed volume of oxygen (V_{O_2}).

3 | CARDIOVASCULAR REGULATION AND THE DIVE RESPONSE

In the most elite and motivated apneists who can consciously suppress respiratory urges, achieving the longest breath hold while maintaining consciousness rests upon the following two fundamental principles: (i) oxygen storage capacity (increased lung volumes); and (ii) oxygen conservation (central blood flow distribution and attenuated oxidative metabolic rate). The second principle is accomplished in large part from cardiovascular and metabolic adjustments that are ascribed to the mammalian dive response. Indeed, the magnitude of the dive response, represented by the extent of bradycardia, is inversely associated with the reduction in arterial O_2 saturation (Andersson & Schagatay, 1998; Andersson, Liner, Runow, & Schagatay, 2002; Lindholm, Sundblad, & Linnarsson, 1999). Importantly, the mammalian dive response is conventionally characterized by vagally mediated bradycardia and sympathetically mediated splenic and peripheral vasoconstriction (reviewed by Foster & Sheel, 2005; Schagatay, 2009). The integration of both sympathetic and parasympathetic pathways underlies the phylo- and ontogenetic origin of the dive responses (Lemaitre, Chowdhury, & Schaller, 2015).

3.1 | Heart rate response during breath holds in elite apneists

At the latter part of a prolonged breath hold in cold water, heart rate (HR) may reach as low as 20–30 beats min^{-1} in elite apneists (Ferrigno et al., 1997; Schagatay, 2009, 2014; and I. D., personal observations). When a maximal (beginning at total lung capacity) static breath hold is performed without facial cooling, however, the average nadir HR in elite apneists is minimally (~5 beats min^{-1}) below resting baseline values, at ~50–65 beats min^{-1} (e.g. Bain et al., 2015a, 2016a; Perini et al., 2008; Willie et al., 2015). Importantly, many studies report that HR decreases by ~30–50 beats min^{-1} during a dry static breath hold in elite apneists, where baseline HR is depicted from the breath-hold onset, when HR is initially elevated from the large lung volume (Perini et al., 2008). Ultimately, generalization of the bradycardia response to a dry static breath hold must be interpreted carefully, because it varies considerably depending on the initial lung volume at the breath-hold onset, the duration of the breath hold and, when interpreted as a percentage or magnitude decline, the initial 'baseline' chosen.

The teleological benefit of apnoea-associated bradycardia is reduced myocardial oxygen consumption, resulting in a slower rate of total oxygen desaturation. In elite apneists, bradycardia in turn increases maximal breath-hold duration. For example, administration of cardiac-specific β_1-blockade (esmolol), to accentuate reductions in HR, increases the maximal dry static breath-hold duration in elite apneists by ~10% (33 s) compared with a placebo (Hoiland et al., 2017). In the study by Hoiland et al. (2017), arterial oxygen saturations were similar at the breath-hold breaking point, indicating that the increased duration of apnoea with cardiac-selective β_1-blockade was probably associated with reduced oxygen consumption. (The ergogenic effect of β-blockers has not been lost in the competitive apnoea community, leading to its ban in all AIDA and CMAS organized competitions.) Perhaps unsurprisingly, the extent of bradycardia is correlated ($R = 0.65$) with the longest durations of apnoea during competition (Schagatay, 2009, 2010).

3.2 | Mechanisms of breath-hold-induced bradycardia

The magnitude of the bradycardia response to breath holds depends largely on the extent of facial cooling (evidenced by the disparate HR responses to maximal breath holds with and without facial cooling, and in Figure 3) and, to a lesser extent, the level of hypoxia and mean arterial blood pressure (MAP). Most importantly, however, the extent of bradycardia requires the cessation of breathing (Gooden, 1994; Lin, Shida, & Hong, 1983). That is, facial cooling without a breath hold does not cause bradycardia (Folinsbee, 1974; Paulev, 1968; Song, Lee, Chung, & Hong, 1969), and breathing a hypoxic gas causes tachycardia (Kato, Menon, & Slutsky, 1988). Ultimately, initiation of bradycardia from apnoea stems from removal of the phasic tachycardia during inspiration (Kato et al., 1988; Lin et al., 1983) and removal of pulmonary stretch receptor input converging at the nucleus tractus solitarii, i.e. the Hering–Breuer reflex. Given that mental stimulation prevents bradycardia during a breath hold (Ross & Steptoe, 1980), there may also be a supramedullary influence on the HR response. For example, reports exist of sinus arrest from simply thinking of, or preparing for, a breath hold (Wolf, 1978).

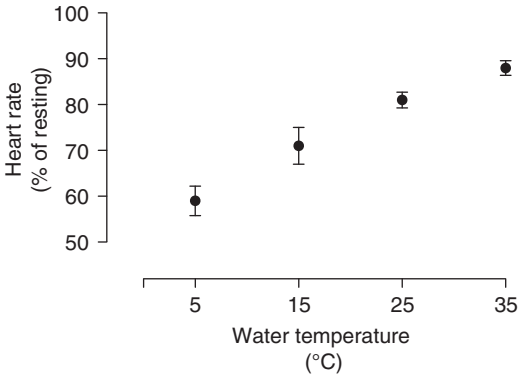

FIGURE 3 Heart rate responses during breath holds with different levels of facial cooling. The magnitude of bradycardia is inversely proportional to the water temperature/facial cooling. Figure adapted from Gooden (1992); data are derived from the average of seven separate studies (see Gooden (1992)

The interacting autonomic control that allows bradycardia during a breath hold is complex, and the exact central pathway remains undefined in humans;however, the topic has received extensive study in animals (Blix & Folkow, 2011; McCulloch, 2012). Ultimately, secondary to the tachycardia 'release' when cyclic pulmonary stretch receptors become dormant, and in combination with potential higher brain centre control, the profound influences of facial cooling, hypoxia and blood pressure point to three important bradycardia-modulating and overlapping reflex pathways: (i) trigeminal nerve activity; (ii) peripheral chemoreceptor activity; and (iii) baroreceptor activity.

3.2.1 | Trigeminal stimulation

Temperature and pain sensation at the face is received through the trigeminal nerve. Descending efferent activity originates from its convergence with the motor nucleus of the vagus nerve (Schaller, 2004). Upon stimulation, the trigeminal nerve initiates a well-established 'trigeminocardiac reflex', characterized by bradycardia, hypotension, gastric hypermobility and cerebrovascular vasodilatation (Schaller et al., 2009). Details of the complete trigeminocardiac reflex have been reviewed recently (Lemaitre et al., 2015), but its central role in the dive response is undoubtedly for bradycardia. The leading influence of trigeminal stimulation on the bradycardia dive response is readily displayed by the different HR responses to breath holding with varying water temperature during facial immersion (Figure 3).

3.2.2 | Peripheral chemoreception

The typical tachycardia response to hypoxia in the spontaneously breathing animal (and human) is contingent upon pulmonary afferent gating, which is removed with apnoea (Kato et al., 1988). Indeed, it is well established that carotid body activation alone (e.g. via isolated hypoxia) causes bradycardia, as described extensively in anaesthetized (e.g. De Burgh Daly & Scott, 1962; de Burgh Daly, Korner, Angell-James, & Oliver, 1978; De Daly & Scott, 1958) and conscious animals

(e.g. Daly & Taton, 1979; Rutherford & Vatner, 1978). Results from animal studies hold true in man. For example, injection of sodium cyanide into the pulmonary artery to stimulate carotid body discharge causes bradycardia (Jain, Subramanian, Julka, & Guz, 1972). Moreover, in five asymptomatic asthmatic patients with bilateral carotid body resection, static breath holds caused tachycardia (Gross, Whipp, Davidson, Koyal, & Wasserman, 1976). In the same study, but with seven healthy control subjects (with intact carotid bodies), bradycardia was attenuated during breath holds performed in hyperoxic conditions that suppressed carotid body activity (Gross et al., 1976). Likewise, in elite apneists, peripheral chemoreflex inhibition with low-dose dopamine attenuates the bradycardia response during dry static breath holds compared with breath holds in the presence of a placebo (Bain et al., 2015a).

The autonomic underpinning for chemoreceptor-mediated bradycardia during a breath hold is best demonstrated from invasive animal work. Specifically, cholinergic blockade with atropine (a muscarinic acetylcholine receptor antagonist) or vagotomy largely removes the bradycardia response to chemoreceptor activation in the dog (De Burgh Daly & Scott, 1962; De Daly & Scott, 1958), cat (Daly & Kirkman, 1989; Macleod & Scott, 1964) and rabbit (Schmidt, Ledderhos, & Honig, 1985), and increased cardiac vagal activity is observed upon chemoreceptor stimulation in the dog (Davis, McCloskey, & Potter, 1977; Jewett, 1964) and cat (Kunze, 1972). These findings indicate vagal activity as the primary pathway for bradycardia upon chemoreceptor stimulation in mammals and are consistent with the seminal work by Heistad, Abbound, and Eckstein (1968), where atropine infusion in humans prevented bradycardia during a 30 s breath hold. However, bradycardia is completely abolished only upon both vagotomy and sympathetic resection to the heart, at least in the dog (De Burgh Daly & Scott, 1962) and cat (Macleod & Scott, 1964), indicating a small role for sympathetic inhibition, albeit results are not consistent with propranolol administration in the monkey (de Burgh Daly et al., 1978). An extensive review of the mechanisms underpinning the cardiac response to chemoreceptor stimulation in mammals is provided elsewhere (Marshall, 1994).

3.2.3 | Blood pressure and baroreception

When a breath hold is prolonged, peripheral vasoconstriction from elevated sympathetic nervous activity progressively leads to an increase in MAP (see section 3.3 Peripheral vasoconstriction). The magnitude of the increase in MAP during a breath hold is variable, but appears similar whether it is performed in dry (out of water) or wet (water immersion) conditions (Breskovic et al., 2011b). [The increase in blood pressure is, of course, accentuated when the breath hold is performed with exercise (Breskovic et al., 2011b; Marongiu et al., 2015).] On average, in elite apneists MAP is increased at the termination of a static dry breath hold (>5 min) by 35–55% (absolute up to ~160 mmHg) from supine resting values (Bain et al., 2015a; Breskovic et al., 2011b; Willie et al., 2015), resulting from elevations in both systolic and diastolic pressure (Breskovic et al., 2011b; Perini et al., 2008). Importantly, these increases in blood pressure are likely to contribute to the reductions in HR through an active baroreflex

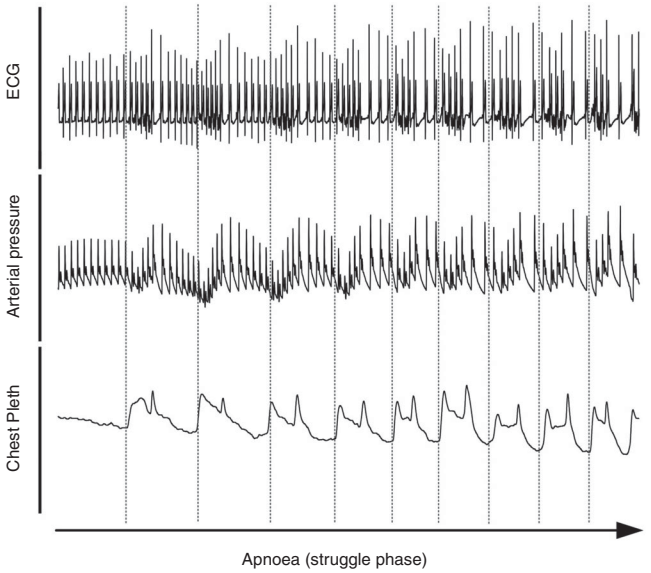

FIGURE 4 Typical trace of the latter part of a breath hold, demonstrating the cardiovascular effects of involuntary breathing movements (IBMs). The IBMs are displayed from the chest wall displacement [chest plethysmograph (pleth), bottom trace] that cause surges in arterial blood pressure (intra-radial, second bottom trace) and irregularities in heart rate (electrocardiogram; ECG, top trace). Dashed vertical lines align the onset of the IBMs

(Perini et al., 2008). Although Gooden (1994) reported no relationship between the increase in arterial blood pressure and HR during breath holds with facial cooling, it appears that apnoea alone does not affect the bradycardic response to neck suction (baroreceptor loading via neck suction at the level of the carotid baroreceptors; Muenter Swift et al., 2003).

Evidence for a baroreflex contribution to the HR response during breath holding is suspected by examining the phasic HR responses throughout a dry static breath hold in elite apneists. Perini et al. (2008) divided the HR responses into three distinct phases: an initial reduction (phase I), plateau (phase II) and further reduction (phase III). Importantly, phase III coincides with the onset of IBMs and concomitant increase in MAP. Indeed, in elite apneists IBMs cause transient increases in venous return and arterial pressure (Dujic et al., 2009), brought on by increased inferior vena caval flow (Palada et al., 2008). The effect of IBMs on the MAP and HR responses is depicted in Figure 4. Alignment of the IBMs with MAP and HR ultimately highlights an operating baroreflex from both atrial and arterial baroreceptors.

A fourth (preceding) HR phase can also be described at the immediate onset of a maximal elite breath hold when performed at total lung capacity. Here, an initial tachycardia response is observed, coinciding with the initial transient reduction in MAP. That is, in elite apneists, a compressing effect of the inflated lungs around the heart upon deep inspiration before the onset of a breath hold causes stroke volume to decrease by ~50% of resting values (Batinic et al., 2011) and MAP to decrease by ~20% (Figure 5), causing acute baroreceptor unloading and an increase in HR (Heusser et al., 2010). The reduction in arterial blood pressure is, of course, exacerbated with glossopharyngeal insufflation (lung packing) where, after a full

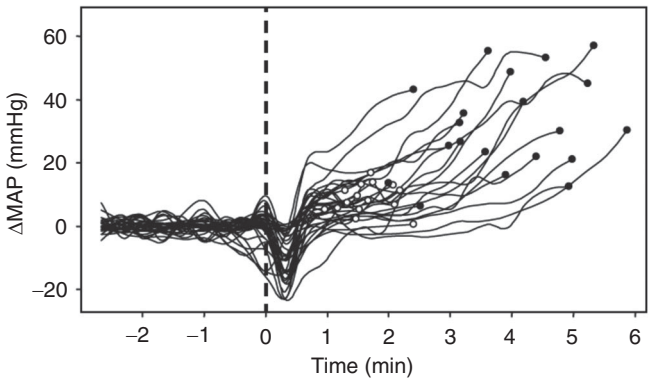

FIGURE 5 Mean arterial pressure responses during static dry breath holds in trained (filled circles) and untrained (open circles) apneists. Figure adapted, with permission, from Heusser et al. (2009). The initial reduction in blood pressure at the onset of the breath hold is attributed to the compressing effect of the inflated lungs around the heart, causing a transient reduction in stroke volume

inspiration, apneists use their glossopharyngeal muscles to pack an additional ~24% of air volume on top of 'normal' total lung capacity (Batinic et al., 2011). With glossopharyngeal insufflation, left and right end-diastolic filling volumes are dramatically reduced, and left ventricular ejection fraction may decrease to 30% (Batinic et al., 2011; Potkin, Cheng, & Siegel, 2007). It is therefore not surprising that symptomatic hypotension is often observed at the onset of competitive apnoea (Dzamonja et al., 2010; Ferrigno, Hickey, Liner, & Lundgren, 1986; Liner, 1994; and A. R. B., unpublished observations). The haemodynamics at the onset of a maximal breath hold after a full inspiration can largely be compared with the second phase of a Valsalva manoeuvre, where, upon increased intrathoracic pressure, the ensuing decrease in venous return, cardiac output and aortic pressure elicits a reciprocal increase in HR from the aortic baroreceptors (Porth, Bamrah, Tristani, & Smith, 1984).

3.3 | Peripheral vasoconstriction

Peripheral vasoconstriction during a breath hold is primarily at the level of the skin and skeletal muscle (Ferretti, 2001), but also in the heart, kidney and spleen (Baković et al., 2003; Kyhl et al., 2016; Mijacika et al., 2017). Interestingly, liver blood flow seems to be maintained (Kyhl et al., 2016), at least during ~3 min static dry breath holds at total lung capacity with glossopharyngeal insufflation.

Evidence for skeletal muscle vasoconstriction in the diving mammal is best demonstrated from the landmark experiment by Scholander in 1940 (reviewed by Blix & Folkow, 2011). In this elegantly simple experiment, Scholander described how a lacerated skeletal muscle in the seal does not bleed when the face is underwater but does bleed when the the seal is breathing. In humans, peripheral vasoconstriction during breath holding remains best described by the early study of Heistad et al. (1968), who demonstrated how blood flow, measured using venous occlusion plethysmography, decreases in the limbs [in the finger from ~21.0 to 13.5 ml min^{-1} (100 ml of tissue)$^{-1}$] during dry static breath holds lasting 30 s, concurrently with increases in arterial pressure (measured directly via intrabrachial cannulation), indicating that the reduced blood flow had to occur from reduced compliance rather than decreased perfusion pressure. Consistent with a conserved dive reflex in humans, the decrease in limb (forearm and finger) blood flow was greater when breath holds were performed with facial cooling (Heistad et al., 1968).

In the same study, Heistad et al. (1968) also established that peripheral vasoconstriction occurred primarily from increased sympathetic activity, because infusion of atropine did not impact the vasoconstrictor response (despite preventing the breath-hold bradycardia that is primarily mediated by the vagus, as discussed earlier). More recent data in elite apneists corroborate increased sympathetic nervous activity as being chiefly responsible for increased peripheral vasoconstriction and decreased peripheral blood flow (Heusser et al., 2009; Steinback, Salmanpour, Breskovic, Dujic, & Shoemaker, 2010b). Importantly, however, the magnitude of peripheral vasoconstriction and blood flow centralization varies markedly depending on breath-holding conditions.

Not surprisingly, the magnitude of the increase in muscle sympathetic nerve activity (measured via microneurography) is largest when a breath hold is combined with facial cooling (Fagius & Sundlöf, 1986; Shamsuzzaman et al., 2014). Still, muscle sympathetic nerve activity (burst frequency and amplitude) markedly increases during a maximal dry static breath hold by an astounding ~2000% from baseline (Heusser et al., 2009; Steinback et al., 2010b). In part because the increase in sympathetic nerve activity is dependent on the duration of breath hold, the primary stimulus for the large sympathetic response during a maximal dry breath hold was initially suggested to result from chemostress (Heusser et al., 2009); however, it is more likely that mounting pulmonary nerve activity is largely responsible (Badrov et al., 2017). Thus, ventilation *per se* partly restrains sympathetic axonal recruitment even during extreme chemoreflex stress (Badrov et al., 2017). Moreover, breath holds performed at different lung volumes will dramatically impact muscle sympathetic nervous activity (Breskovic, Steinback, Salmanpour, Shoemaker, & Dujic, 2011a; Dujic et al., 2008; Heusser et al., 2009, 2010; Steinback, Breskovic, Banic, Dujic, & Shoemaker, 2010a; Steinback et al., 2010b) and central blood flow distribution (Stembridge et al., 2017).

As classically described, the functional role for peripheral vasoconstriction during a breath hold is to prioritize oxygen-rich blood flow to the brain and to attenuate the decline in oxygen saturation by increasing circulating haemoglobin concentration through splenic contractions (Espersen, Frandsen, Lorentzen, Kanstrup, & Christensen, 2002) and by forcing the hypoxic skeletal muscle tissue towards non-oxidative metabolism (Ferretti, 2001). This latter non-oxidative metabolic response might play a leading role in oxygen conservation during dynamic/diving breath holds (Andersson & Evaggelidis, 2009; Andersson, Liner, Fredsted, & Schagatay, 2004; Marongiu et al., 2015). However, evidence for a shift towards non-oxidative skeletal muscle metabolism during a dry static breath hold in elite apneists is less evident. For example, in considering increases in plasma lactate as a rough proxy for increases in non-oxidative metabolism (from the anaerobic conversion of pyruvate to lactate), an increase in anaerobic metabolism is likely to be minimal given that circulating lactate increases only modestly by ~0.3 mmol l^{-1} (absolute at ~1.3 mmol l^{-1})

during dry static breath holds lasting ~5 min (Bain et al., 2016a, 2017a). In comparison, plasma lactate may increase to ~4 mmol l^{-1} during depth dives to 30 m (Marongiu et al., 2015) and >10 mmol l^{-1} during strenuous exercise (van Loon, Greenhaff, Constantin-Teodosiu, Saris, & Wagenmakers, 2001).

The concept of spleen contraction is often described as a property of the diving response (Espersen et al., 2002). The spleen serves as a dynamic blood cell reservoir, and in humans contains ~200–250 ml of densely packed blood cells and ~8% of the total body red blood cell pool [Koga, 1979; in contrast, in seals the spleen contains up to ~50% of the total body red blood cell count (Hurford et al., 1996)]. Contraction of the spleen can thus increase circulating haemoglobin and haematocrit to enhance oxygen transport during a breath hold, a reflex that is lost after splenectomy (Baković et al., 2005; Lodin-Sundström & Schagatay, 2010; Schagatay, Andersson, Hallen, & Palsson, 2001). The magnitude of splenic contraction depends on the duration of the breath hold and whether the breath hold is performed underwater or with facial cooling (Espersen et al., 2002). At the termination of a ~5 min dry static breath hold in elite apneists, splenic contraction causes circulating venous haemoglobin and the haematocrit to increase by ~4% (Bain et al., 2016a, 2017a). Meanwhile, following five consecutive static breath holds with the face immersed in cold water (with 2 min rests in between breath holds), the plasma volume-corrected red blood cell volume and the venous concentration of white blood cells increased by 5 and 15%, respectively (Baković et al., 2005). The rapidity of splenic contraction during a breath hold (Palada et al., 2008) indicates that the initial stimulation is likely to be neural in origin, owing to sympathoexcitation (Bakovic et al., 2013). Splenic contraction may be sustained throughout a breath hold by circulating catecholamines released from the adrenal gland and by delayed changes in the arterial blood gases (hypoxia and hypercapnia; Baković et al., 2005). A mechanical compression after inhalation of a large volume of air may also contribute to rapid splenic contraction during a breath hold (Palada et al., 2008).

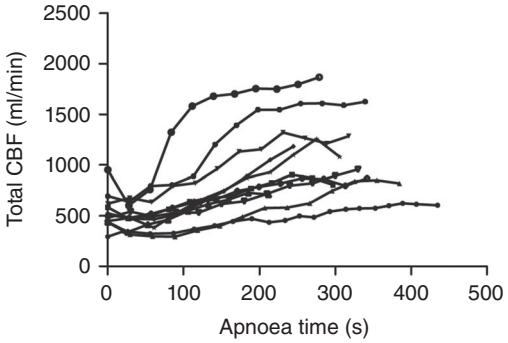

FIGURE 6 Cerebral blood flow (CBF), derived by duplex ultrasound of the internal carotid and vertebral arteries, response during a dry static breath hold in elite apneists. Figure adapted, with permission, from Willie et al. (2015). Interestingly, the subject with the longest breath-hold duration had the smallest increase in CBF, attributed in part to profound glossopharyngeal insufflation in this subject

4 | CEREBROVASCULAR REGULATION

4.1 | Cerebral blood flow

The high metabolic demand and bleak energy store of the brain make hypoxaemia a critical challenge for cerebral functioning. No better is this exemplified than by the fact that complete and abrupt cessation of cerebral oxygen supply results in unconsciousness within 4–6 s (Smith, Clayton, & Robertson, 2011) and brain death within a few minutes. Cerebral blood flow (CBF) regulation during hypoxaemia is thus paramount to maintain cerebral oxygen delivery (Hoiland, Bain, Rieger, Bailey, & Ainslie, 2016). The regulation of CBF is by vasomotor, chemical, metabolic and neurogenic mechanisms and by factors that change the prevailing perfusion pressure, vascular resistance and surrounding pressures (Donnelly, Budohoski, Smielewski, & Czosnyka, 2016; Willie, Tzeng, Fisher, & Ainslie, 2014). All of these interacting CBF regulatory systems are dynamically active during apnoea. The net result during a dry static breath hold in most elite apneists is a peak increase in global CBF by ~70 to 110% (Figure 6) from resting levels, as determined by concomitant transcranial Doppler imaging of the internal carotid and vertebral arteries (Bain et al., 2015a; Bain et al., 2016b; Bain et al., 2017a; Willie et al., 2015). Notably, however, the increase in CBF varies considerably (see Figure 6). Moreover, from a methodological standpoint, the reported change in CBF throughout a maximal dry static breath hold will be greater if the 'baseline zero' is chosen immediately before the onset, coinciding with the immediate deep breaths that cause mild hypocapnia and reductions in true 'baseline' CBF.

An increase in CBF throughout a breath hold occurs largely from hypercapnia- and hypoxaemia-induced pial artery dilatation in combination with hypertension and the subsequent increases in perfusion pressure (Bain et al., 2015a, 2016b; Cross et al., 2013b; Stembridge et al., 2017; Willie et al., 2015). However, the mechanisms responsible for increasing the CBF are in continual competition with CBF-attenuating factors, including profound sympathoexcitation and increased intracranial pressure (ICP) (see Figure 7). The vasoconstrictor impact of cerebral sympathoexcitation during apnoea remains speculative, but might prevent cerebral haemorrhaging associated with the large increases in cerebral blood volume (Brassard, Tymko, & Ainslie, 2017) and arterial pressure. Indeed, measures of subarachnoid width (Winklewski et al., 2015) and internal jugular venous pressure (IJVP; Figure 7; Bloomfield, Ridings, Blocher, Marmarou, & Sugerman, 1997; Stembridge et al., 2017) during static breath holding in elite apneists suggest notable increases in ICP [IJVP is strongly correlated with direct measures of ICP in humans (Myerson & Loman, 1932)]. It is speculated that intrathoracic vessel (e.g. superior vena cava) compression from high lung volumes, in combination with transient surges in intrathoracic pressure from IBMs (Cross et al., 2013a; Winklewski et al., 2015) collectively increase the ICP by reducing the passive pressure gradient for cerebral venous drainage (Stembridge et al., 2017). Mathematelically, an increase in ICP will result in reduced cerebral perfusion pressure (CPP; i.e. CPP = MAP − ICP). However, in the study by Stembridge et al. (2017), marked increases in ICP (determined by the surrogate measure of IJVP) during the last

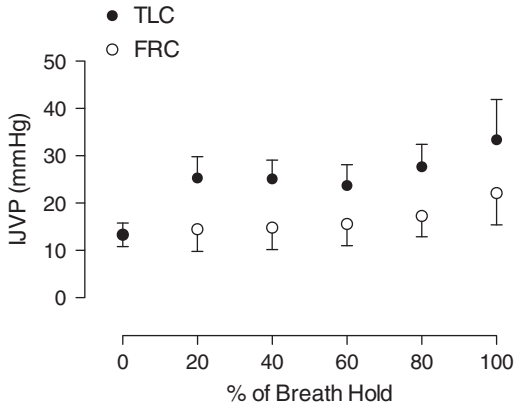

FIGURE 7 Internal jugular venous pressure (IJVP) throughout a maximal dry static breath hold performed at functional residual capacity (FRC; open circles), and total lung capacity (TLC; filled circles). The increased IJVP is largely attributed to compression of the intra-thoracic vessels from high lung volumes and is excacerbated by involuntary breathing movements after 60% of the breath hold. Figure adapted from Stembridge et al. (2017)

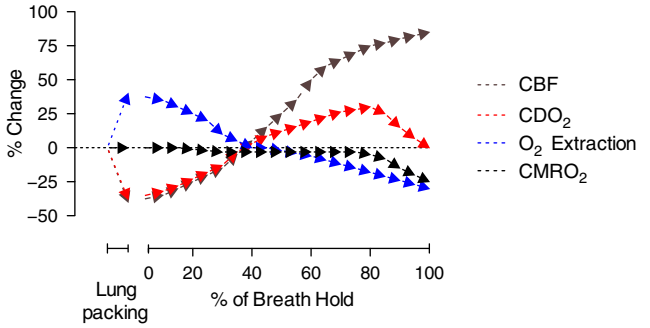

FIGURE 8 A schematic diagram presenting typical percentage changes in cerebral blood flow (CBF in gray), cerebral oxygen delivery (CDO_2 in red), cerebral oxygen extraction (O_2 Extraction in blue) and the cerebral metabolic rate of oxygen ($CMRO_2$ in black) throughout maximal dry breath holds of ~5 min or longer in elite apneists, performed with glossopharyngeal insufflation (lung packing). At the initial stages of the breath hold, CBF and CDO_2 are depressed below baseline resting values, primarily attributable to the hypotension and hypocapnia subsequent to glossopharyngeal insufflation. The $CMRO_2$ is maintained at the apnoea onset owing to the increased cerebral O_2 extraction. The reduction of $CMRO_2$ at the latter end of the breath hold is primarily attributed to the hypercapnia. Data averaged from Bain et al. (2015a, 2016a, 2017a) and Willie et al. (2015). See main text for detail

quarter of a maxmial breath hold coincided with surges in systolic pressure/MAP, which prevented a decrease in CPP. This finding was suggested to indicate a Cushing reflex (Cushing, 1901). A possible mechanism that could theorethically minimize the increase in ICP during a maximal breath hold is a cranial to spinal shift in cerebral spinal fluid; however, whether this occurs is presently unknown.

It is clear that cerebrovascular regulation during breath holding is complicated through an integration of factors. The determination of cerebral autoregulation, i.e. the umbrella term explaining the cerebrovascular resistance responses to changes in CPP, is thus difficult to ascertain in apnoea. For example, when determined by simple pressure (MAP) and flow (CBF) slopes, cerebral autoregulation is seemingly intact during prolonged apnoea (Willie et al., 2015). Here, despite further increases in MAP with apnoea, the elevations in CBF are attenuated (probably via increases in ICP). In contrast, when reported using a transfer function analysis (Cross, Kavanagh, Breskovic, Johnson, & Dujic, 2014), cerebral autoregulation appears impaired. Nonetheless, a caveat to both studies is the negation of ICP in determining the CPP. The additional consideration in using transfer function analysis is that the analyses, based on transcranial Doppler and blood pressure, assume both linearity and stationarity between the estimates of flow and pressure (Tzeng & Ainslie, 2014). Given that apnoea is both non-linear and non-stationarity in nature, these assumptions are not met.

4.2 | Cerebral oxygen delivery

Except at the onset of a breath hold, when the CBF is transiently reduced below baseline levels (owing to the reductions in MAP and hypocapnia), the global cerebral delivery of oxygen (CDO_2) during a static dry breath hold quickly recovers to values above baseline, even despite a ~50% reduction in arterial oxygen saturation (Figure 8; Bain et al., 2015a, 2016b, 2017a; Willie et al., 2015). However, regional or local impairments in the CDO_2 remain unknown and are certainly possible given the known P_{O_2} gradients in brain tissue (reviewed by Ainslie, Hoiland, & Bailey, 2016). For example, deeper brain regions may become more hypoxic than the superficial regions (Dunn & Swartz, 1997). The global CDO_2 above metabolic needs throughout the mid-sections of a maximal dry static breath hold is a consequence of the hypercapnia and hypertension that increases CBF beyond the effects of hypoxaemia alone.

4.3 | Cerebral oxidative metabolism

Throughout the majority of a dry static maximal breath hold in elite apneists, the cerebral metabolic rate of oxygen ($CMRO_2$) remains unaltered (Figure 8; Bain et al., 2016a, 2017a). However, immediately before the breaking point of dry static breath holds lasting on average >5 min, $CMRO_2$ appears to be reduced by ~25% (from ~48 to 36 ml min^{-1}; Bain et al., 2016a, 2017a). It is suspected that the reduced $CMRO_2$ reported by Bain et al. (2016a, 2017a) might be dependent on the level of hypercapnia. For example, the $CMRO_2$ remains relatively unchanged at the breaking point of static breath holds performed after pronounced hyperventilation [pre-apnoea arterial partial pressure of carbon dioxide (P_{aCO_2}) ~20 mmHg], because the absolute peak P_{aCO_2} achieved is scarcely above eucapnia (Bain et al., 2017a). Moreover, reductions in $CMRO_2$ observed near the termination of a maximal dry static breath hold are correlated with the highest P_{aCO_2} (Figure 9). A candidate mechanism for the cerebral hypometabolic effects of hypercapnia is through increased activation of adenosine A_1 receptors and inhibition of excitatory glutamatergic neurotransmission (Dulla et al., 2005). With a background of oxygen deprivation, activation of adenosine A_1 receptors may also directly inhibit mitochondrial

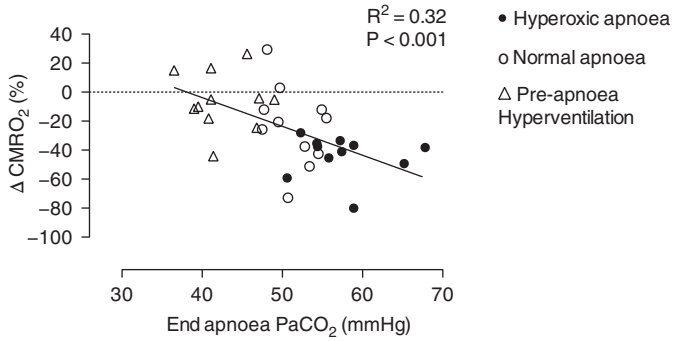

FIGURE 9 Changes in cerebral metabolic rate of oxygen ($CMRO_2$) over the peak partial pressures of arterial carbon dioxide (P_{aCO_2}) during dry static breath holds. Breath holds were performed with prior 100% oxygen breathing (hyperoxic apnoea; filled circles), in normal conditions (open circles) and with prior hyperventilation (pre-apnoea hyperventilation; triangles). The magnitude of change in $CMRO_2$ is correlated with the absolute level of P_{aCO_2} at the breath-hold end. Figure adapted from Bain et al. (2017a)

metabolism (Duarte, Cunha, & Carvalho, 2016). Moreover, hypercapnia might attenuate the $CMRO_2$ by reducing phosphofructokinase-1 activity (Folbergrová, Norberg, Quistorff, & Siesjö, 1975).

Large increases in CBF could also depress the $CMRO_2$ via reductions in cerebral temperature, given that the arteriovenous temperature gradient across the brain is generally negative (reviewed by Bain, Nybo, & Ainslie, 2015b). A thermal mechanism for reductions in $CMRO_2$ during a dry static breath hold in humans is probably negligible, but might be relevant when a breath hold is performed in cold water. Interestingly, seals are able to reduce their body core and brain temperature by ~2.5°C during a 20 min breath hold in 4°C water (Blix, Walløe, Messelt, & Folkow, 2010). According to the Q_{10} of biological tissue, this alone would reduce metabolism by ~25% (Bain et al., 2015b). A reduction in body temperature is certainly beneficial in these circumstances of extreme breath holding.

In contrast to findings by Bain et al. (2016a, 2017a), a recent study by Vestergaard & Larsson (2017) reported no changes in $CMRO_2$ throughout dry static breath holds in elite apneists. These divergent findings are perhaps explained by methodological differences. For example, in the studies by Bain et al. (2016a, 2017a) $CMRO_2$ was calculated directly from arteriovenous oxygen differences measured through invasive cannulation of the radial artery and internal jugular vein, concurrently with global cerebral blood flow measured from duplex ultrasound of the internal carotid and vertebral artery. In contrast, the $CMRO_2$ in the study by Vestergaard and Larsson (2017) was estimated from magnetic resonance imaging and with sagittal sinus blood flow used as a proxy for global cerebral blood flow. Both techniques rely on the Fick principle, where the $CMRO_2$ is ultimately calculated from cerebral arteriovenous oxygen content differences, multiplied by the blood flow. However, the increase in sagittal sinus blood flow in the elite breath holds reported by Vestergaard and Larrson (2017) was much higher than the increase in global CBF reported by Bain et al. (2016a, 2017a); ~144 *versus* ~80%, respectively. Importantly, phase contrast mapping as used by Vestergaard and Larsson (2017) has been shown to overestimate CBF by up to ~63% compared with blood flow measured from ^{15}O-H_2O positron emission tomography, especially when measured in areas where smaller vessel contamination is possible, which is a high probability when measuring blood flow at the sagittal sinus (Vestergaard et al., 2017). Differences in experimental design might additionally explain the discrepant findings of Vestergaard and Larsson (2017) compared with the studies by Bain et al. (2016a, 2017a). Preparatory breath holds were permitted by Bain et al. (2016a, 2017a), and average breath holds were ~20 s longer compared with the average of the nine longest measured by Vestergaard and Larsson (2017). Moreover, P_{aCO_2} was not determined by Vestergaard and Larsson (2017), and pre-breath-hold hyperventilation was suspected in the longest breath holds. That $CMRO_2$ remained unchanged with the few longest breath holds in Vestergaard and Larsson (2017) may therefore reflect, in part, minimal absolute increases in P_{aCO_2} above eucapnia, completely consistent with findings reported by (Bain et al., 2017a).

4.4 | Cerebral non-oxidative metabolism

In the cerebral tissue, there appears to be no increase in non-oxidative metabolism, at least during breath holds without facial water immersion. Specifically, the ratio of oxygen and carbohydrate consumption in the brain (the oxidative carbohydrate index) remains unchanged throughout a maximal dry static breath hold in elite apneists (Bain et al., 2016a, 2017a). Unaltered non-oxidative metabolism as determined by magnetic resonance imaging in the occipital lobe during an elite dry static breath hold has also been reported (Vestergaard & Larsson, 2017).

5 | PHYSIOLOGICAL ADAPTATIONS WITH BREATH-HOLD TRAINING

Performing a voluntary breath hold for well over 5 min ultimately stems from genetic attributes (Eftedal, Flatberg, Drvis, & Dujic, 2016) combined with the psychophysical and physiological factors that are modifiable with training. Figure 10 provides an encompassing schematic diagram of the mechanisms and processes associated with training and preparation that contribute to prolonging a maximal static breath-hold duration. Increased motivation, improved relaxation techniques and stress tolerance certainly underscore

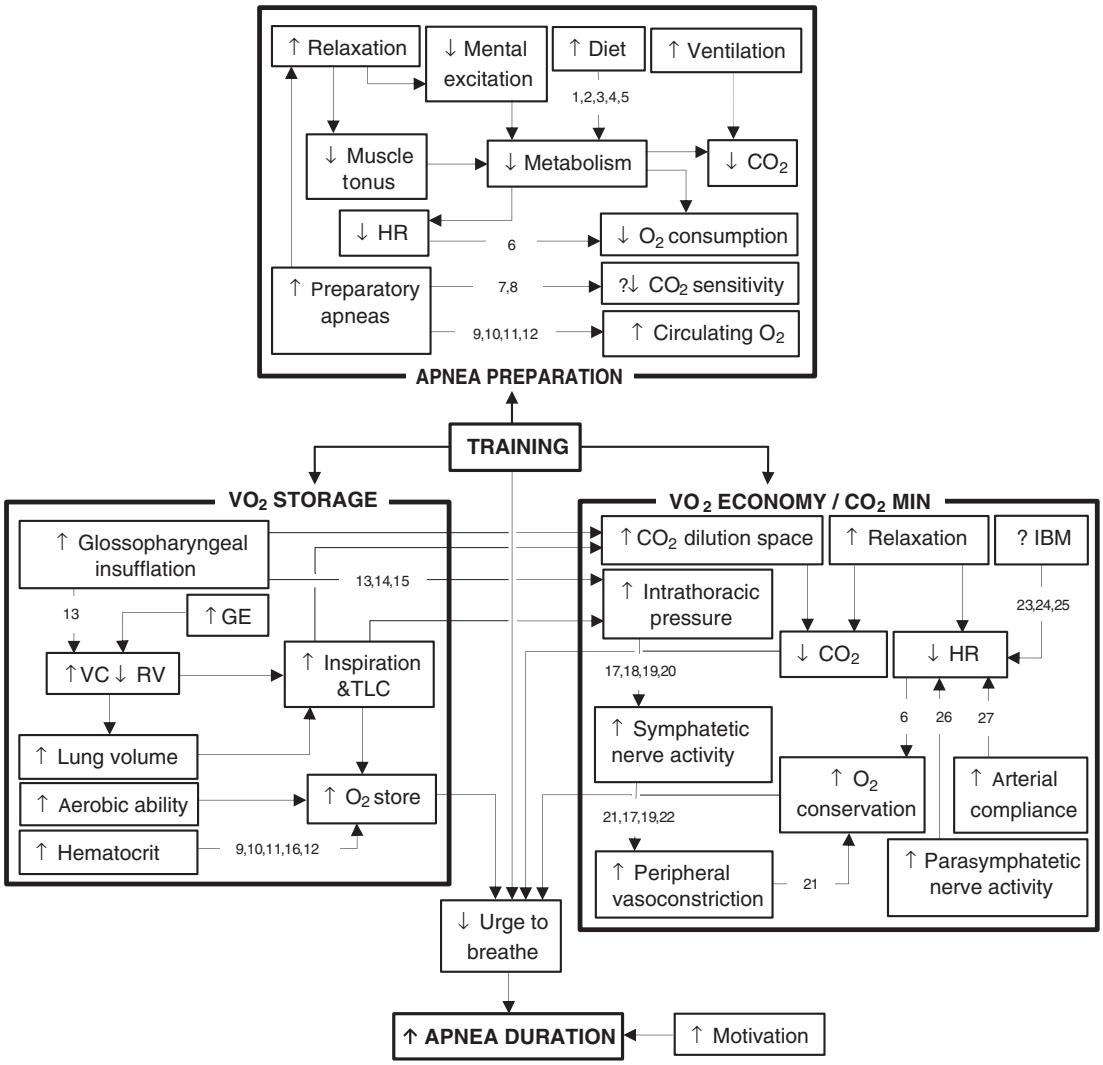

FIGURE 10 Adaptations with breath-hold training. The maximal static breath-hold duration is primarily determined by the following factors: Preparation, maximal oxygen storage ability (V_{O_2} storage), minimal oxygen consumption (V_{O_2} economy), minimal CO_2 accumulation (CO_2 min) and, importantly, motivation. Arrows down (↓) and up (↑) within the framed boxes indicate a decrease or increase of the associated variable. Other abbreviations: GE, glossopharyngeal exufflation; HR, heart rate; IBM, involuntary breathing movements; RV, residual volume; TLC, total lung capacity; and VC, vital capacity. Supporting literature is denoted by the numbers, where: 1 = Engan et al. (2012); 2 = Ghiani et al. (2016); 3 = Lindholm et al. (2007); 4 = Schagatay and Lodin-Sundström (2014); 5 = Patrician and Schagatay (2017); 6 = Hoiland et al. (2017); 7 = Ivancev et al. (2007); 8 = Walterspacher et al. (2011); 9 = Bakovic et al. (2005); 10 = Bakovic et al. (2003); 11 = Schagatay et al. (2001); 12 = Espersen et al. (2002); 13 = Overgaard et al. (2006); 14 = Eichinger et al. (2010); 15 = Batinic et al. (2011); 16 = Lodin-Sundström and Schagatay (2010); 17 = Heusser et al. (2009); 18 = Steinback et al. (2010a); 19 = Steinback et al. (2010b); 20 = Breskovic et al. (2011a); 21 = Dujic et al. (2008); 22 = Heistad et al. (1968); 23 = Dujic et al. (2009); 24 = Palada et al. (2008); 25 = Willie et al. (2015); 26 = Lemaitre et al. (2015); and 27 = Tanaka et al. (2016)

increased breath-hold times with apnoea training (Ostrowski et al., 2012). Nonetheless, the major physiological factors that can improve maximal breath-hold duration, and reportedly modified with training, also include increasing lung size (and therefore oxygen storage capacity) through practised glossopharyngeal insufflation, and cardiovascular/haemodynamic adjustments that can attenuate the rate of oxygen desaturation. Although less clearly defined, adaptations in the chemoreflex (respiratory response to CO_2 and O_2) may also occur with apnoea training. These major physiological adjustments in trained apneists are briefly discussed below. Although only mentioned and not discussed here, other trainable/practised components that can improve maximal breath-hold duration include preconditioning (preparatory apnoeas) and relaxation techniques to attenuate oxygen consumption. Dietary restrictions (fasting; Lindholm, Conniff, Gennser, Pendergast, & Lundgren, 2007; Schagatay & Lodin-Sundström, 2014) and supplementation (nitrate; Engan, Jones, Ehrenberg, & Schagatay, 2012; Patrician & Schagatay, 2017) can also contribute to increasing a maximal breath-hold duration (Figure 10).

5.1 | Lung volume adaptations

The ability to pack more air in the lungs attenuates the rate of blood oxygen desaturation during a breath hold, dilutes CO_2 in the lungs (Schagatay, 2009), lessens diaphragmatic stress associated with

reduced lung volumes and prevents lung collapse in depth dives (Overgaard, Friis, Pedersen, & Lykkeboe, 2006). In keeping, it is generally accepted that trained apneists have larger lung volumes (Ferretti & Costa, 2003). Although this may be, in part, an inherent characteristic of elite apneists, increased lung volumes (or forced vital capacity) seems to occur from practised glossopharyngeal insufflation and strengthened respiratory muscles (Ferretti & Costa, 2003). That is, apneists train through chest stretching exercises with 'packed lungs', as well as reverse 'packing' (forced exhalation; glossopharyngeal exufflation) to decrease the residual volume. Indeed, Schagatay (2014) reported that 11 weeks of apnoea training increases vital capacity by 0.45 litres. Moreover, vital capacity is on average 1.8 litres larger in practised apneists than in age- and size-matched control subjects (Schagatay, 2014), and trained US Navy skin divers have a ∼15% larger vital capacity compared with untrained control subjects (Carey, Schaefer, & Alvis, 1956). Ama divers have also been reported to have a ∼15% higher vital capacity than their non-diving counterparts (original studies reviewed by Ferretti & Costa, 2003). However, a more recent and robust study of 115 Ama divers compared with 33 healthy matched control subjects reported no differences in vital capacity (Tanaka, Tomoto, Kosaki, & Sugawara, 2016). These latter findings may, in part, relate to the distinct breathing patterns in shellfish divers compared with today's competitive apneists, whereby glossopharyngeal insufflation is generally avoided in the Ama (Tanaka et al., 2016).

5.2 | Cardiovascular adaptations and the dive response

The description of an accentuated dive response in trained apneists is often complicated by the fact that the absolute magnitude of decline in HR and increase in MAP is dependent on the duration of the breath hold (Perini et al., 2008). However, it is generally accepted that trained apneists have a larger dive response compared with untrained control subjects, as described by a greater magnitude heart rate reduction and larger increase in blood pressure (reviewed by Ostrowski et al., 2012). For example, Engan, Richardson, Lodin-Sundström, van Beekvelt, & Schagatay (2013) report that after 2 weeks of apnoea training in previously naive healthy subjects, diving bradycardia develops earlier (∼3 s) and the rate of arterial oxygen desaturation is attenuated (nadir arterial oxygen saturation at end breath hold of 84 *versus* 89%), importantly in breath holds of identical duration and with similar starting lung volumes (i.e. controlled mimicked breath holds).

The mechanistic explanation for an accentuated dive response in trained apneists remains difficult to ascertain. It has been reported recently that Ama divers have greater central (aortic) arterial compliance compared with age-, body mass index- and activity level-controlled counterparts living in the same community (Tanaka et al., 2016). In the Ama, it was speculated that the circulatory stress and increased cardiac pulsation during breath holds fosters improved arterial elasticity, which may promote a greater bradycardia response to diving via more active baroreception (Tanaka et al., 2016). Altered arterial stiffness from apnoea training, however, is not consistently reported (Steinback et al., 2010a). For example, Steinback et al. (2010a) reported that spontaneous assessment of the cardiovagal baroreflex gain is similar in trained apneists compared with untrained control subjects. These discrepant findings may, in turn, highlight an adaptation in Ama from a lifetime of performing repeated breath holds, *versus* competitive apneists with only ∼5 years of training. Future cross-sectional and longitudinal study on the cardiovascular adjustments in trained apneists warrants attention.

An increase in CBF is essential to maintain the cerebral oxygen delivery during progressive hypoxaemia associated with prolonged breath holds. However, there seems to be little evidence of improvements or adaptations in cerebrovascular function. For example, CO_2 reactivity is similar in trained *versus* untrained apneists (Ivancev et al., 2007). It was recently reported that apneists had a higher cerebrovascular reactivity to hypoxaemia, but only when assessed from sagittal sinus blood flow and not when indexed from global CBF via phase contrast images of the internal carotid and basilar artery (Vestergaard & Larsson, 2017). Although it remains possible that local or regional differences exist, the study by Vestergaard and Larsson (2017) should be interpreted cautiously since sub-par methods to assess cerebrovascular reactivity were employed, i.e. use of fixed inspired gas manipulation (rather end-tidal clamping), hence non-steady-state and uncontrolled changes in P_{aCO_2} and P_{aO_2}, as well as no account for changes in perfusion pressure and conductance.

It has been suggested that, like diving bradycardia, breath-hold training can accentuate splenic contraction during a breath hold and perhaps also increase baseline spleen size. For example, breath-hold performance has been correlated with the size of the spleen (Schagatay, Richardson, & Lodin-Sundström, 2012), and trained apneists have been reported to have larger spleens than matched control subjects (Schagatay, 2014). Moreover, in trained apneists, five repeated underwater breath holds resulted in a ∼25% reduction in spleen size, whereas spleen size remained unchanged in control subjects after breath holds (Prommer et al., 2007). Red blood cell volume and the venous concentration of white blood cells have also been reported to increase to a greater extent in trained *versus* untrained apneists after breath holds (Baković et al., 2005). An important consideration, however, is that breath-holding time in trained apneists is always longer than in the untrained apneists. Importantly, Espersen et al. (2002) reported no differences in splenic contraction after identical breath-hold durations in trained *versus* untrained apneists.

5.3 | Chemoreflex adaptations

As reviewed elsewhere (Ferretti, 2001), it is generally believed that the ventilatory response to CO_2 (Grassi et al., 1994; Ivancev et al., 2007; Masuda, Yoshida, Hayashi, Sasaki, & Honda, 1981; Walterspacher, Scholz, Tetzlaff, & Sorichter, 2011) and (to a lesser extent) hypoxia (Masuda et al., 1981; Walterspacher et al., 2011) is depressed in trained apneists, but this is not a consistent finding of all studies (Breskovic, Ivancev, Banic, Jordan, & Dujic, 2010; Dujic et al., 2008; Grassi et al., 1994). A depressed ventilatory response adjustment to CO_2, in particular, would prolong the onset time before IBMs, increasing the easy-going phase of a prolonged breath hold. The discrepancy in the reported studies might reflect the experimental

burden of dissociating improved conscious tolerance to chemostress *versus* a fundamental physiological change in the chemoreflex. The former (increased tolerance) is certainly accentuated in trained apneists; however, future 'stimulus-blinded' studies are required to establish the extent of a physiological chemoreflex adjustment in trained apneists.

6 | MALADAPTATIONS WITH APNOEA TRAINING

The acute dangers associated with competitive apnoea are apparent and should not be underestimated, e.g. lung injury associated with glossopharyngeal insufflation (Chung et al., 2010; Mijacika & Dujic, 2016), barotrauma, syncope, drowning and shallow water blackout during depth dives (Lindholm & Lundgren, 2009); as well as cardiac arrest, especially when breath holds are performed in cold water (Hong, Song, Kim, & Suh, 1967). The longer-term health impacts of competitive static breath holding, however, remain less understood.

Conceptually, the effects of cyclic hypoxia in apnoea participants performing >150 dives in a single day (e.g. in the Ama, during recreational spear fishing or apnoea practice) may certainly mirror some of the consequential physiological changes associated with sleep-disordered breathing. Yet, whereas cerebrovascular CO_2 reactivity is reduced in obstructive sleep apnoea patients (Prilipko, Huynh, Thomason, Kushida, & Guilleminault, 2014), it is unchanged in elite apneists (Ivancev et al., 2007). Moreover, as previously mentioned, sympathetic baroreflex gain and respiratory muscle sympathetic nervous activity modulation are also unchanged in trained apneists (Steinback et al., 2010a). Therefore, unlike pathophysiological sleep apnoea (Dempsey, Veasey, Morgan, & O'Donnell, 2010), apnoea competition does not yield autonomic dysregulation. Conversely, long-term neurological problems (especially when related to cerebral decompression sickness after repeated depth breath holds; Kohshi et al., 2014; Matsuo et al., 2014) have been reported. For example, compared with matched control subjects, trained apneists were reported to have slower responses on a Stroop test and more errors on interference card tests (Billaut, Gueit, Faure, Costalat, & Lemaitre, 2018). These findings were correlated with the maximal breath-hold abilities ($r = 0.73$) and years of training ($r = 0.79$), collectively suggesting that apnoea training can cause persistent short-term memory impairments. In further support of cognitive/neuronal impacts of competitive breath holding, peripherally circulating plasma neuron-specific enolase (a marker for acute neuronal damage) is increased after apnoea competition (Kjeld et al., 2015). Moreover, mild (albeit non-pathological) opening of the blood–brain barrier occurs after even a single static maximal breath hold in elite apneists (Andersson, Liner, & Jonsson, 2009; Bain et al., 2018), as evidenced by increased concentrations of circulating S100β, a primarily astrocyte-derived protein that is clinically established to correlate with blood–brain barrier opening (Marchi et al., 2003). Although speculative, mild opening of the blood–brain barrier during apnoea might result from the transient surges in ICP, rather than from the severe hypoxaemia *per se* (Bain et al., 2018). It is clear that more longitudinal research is required to understand the long-term maladaptations of competitive breath holding, especially as they relates to the cerebral parenchymal and cognitive health. Nevertheless, emerging evidence suggests that apnoea competition can negatively impact long-term cerebral health, which must be considered given the growing popularity of the sport.

7 | CONCLUSION

Contemporary scientific exploration has provided significant insight to the physiological mechanisms that explain seemingly insurmountable voluntary breath-hold durations in elite apneists. The pertinent physiological characteristics and mechanisms that make extreme breath-holds possible in humans engaged in competitive apnoea have been outlined. A better understanding of these factors that determine breath hold duration is not only relevant to those interested in extreme human physiology, as well as apnoea competition and coaching, but also from a safety and medical standpoint to help better inform CMAS and AIDA guidelines. In this review, we have emphasized the recent data on cerebral vascular and metabolic function during dry-land static breath holds. It remains to be determined whether the addition of facial cooling and thus an accented dive reflex impacts the major cerebral vascular and metabolic responses. Moreover, future cross-sectional and longitudinal study on the potential adaptations and maladaptation are required to further our fundamental understanding of the physiological consequences of regular breath hold competition.

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AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of the work. A.R.B. drafted the manuscript. All authors revised it critically for important intellectual content. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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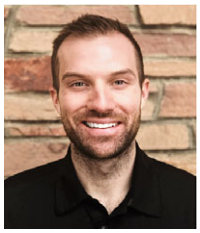

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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