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Cardiovascular responses to dry apnoeas at exercise in air and in pure oxygen

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ABSTRACT

If, as postulated, the end of the steady state phase (φ2) of cardiovascular responses to apnoea corresponds to the physiological breaking point, then we may hypothesize that φ2 should become visible if exercise apnoeas are performed in pure oxygen. We tested this hypothesis on 9 professional divers by means of continuous recording of blood pressure (BP), heart rate (f_H), stroke volume (Q_S), and arterial oxygen saturation (SpO_2) during dry maximal exercising apnoeas in ambient air and in oxygen. Apnoeas lasted 45.0 ± 16.9 s in air and 77.0 ± 28.9 s in oxygen ($p < 0.05$). In air, no φ2 was observed. Conversely, in oxygen, a φ2 of 28 ± 5 s duration appeared, during which systolic BP (185 ± 29 mmHg), f_H (93 ± 16 bpm) and Q_S (91 ± 16 ml) remained stable. End-apnoea SpO_2 was 95.5 ± 1.9% in air and 100% in oxygen. The results support the tested hypothesis.

1. Introduction

A beat-by-beat analysis of the time course of cardiovascular variables during breath-holding (Costalat et al., 2017, 2013; Fagoni et al., 2017, 2015; Hoiland et al., 2017; Lemaître et al., 2008; Perini et al., 2010, 2008; Sivieri et al., 2015; Tocco et al., 2013, 2012) led to the definition of three distinct phases, which were modelled by Costalat et al. (2017, 2015). These phases are: (i) the first short dynamic phase (φ1); (ii) the steady state phase in which the cardiovascular variables are maintained invariant (φ2); and (iii) the final dynamic phase characterised by a continuous decrease in heart rate (f_H) and increase in blood pressure (φ3).

The φ1 is characterised by a sudden fall of arterial blood pressure and of stroke volume (Q_S) (Andersson and Schagatay, 1998; Fagoni et al., 2017, 2015; Perini et al., 2008). These fall may be due to an immediate fall in venous return related to the high lung volumes at which apnoeas are carried out (Andersson and Schagatay, 1998; Novalija et al., 2007). The concomitant f_H increase in φ1 has been attributed to a baroreflex response (Fagoni et al., 2017, 2015; Sivieri et al., 2015). φ1 has a quite constant duration of less than 30 s and its quantitative characteristics are independent of the metabolic rate (Sivieri et al., 2015) and of the size of lung oxygen stores (Fagoni et al., 2015).

Conversely, the physiological meanings of φ2 and φ3 are still unclear. The current conjecture, which is implicitly included in the model of Costalat et al. (2017, 2015), is that the end of φ2 (Fagoni et al., 2017, 2015; Perini et al., 2010; Sivieri et al., 2015) may correspond to the physiological breaking point of apnoea (Agostoni, 1963; Lin et al., 1974). The observations that φ2 becomes longer in apnoeas performed after breathing pure oxygen (Fagoni et al., 2015) and disappears in apnoeas performed during light exercise (Sivieri et al., 2015) agree with this conjecture. If this conjecture is true, we hypothesize that φ2 should become visible if exercise apnoeas are performed during pure oxygen breathing. The aim of our study was to test this hypothesis by performing a beat-by-beat analysis of the cardiovascular responses to exercising apnoea in pure oxygen.

2. Methods

2.1. Subjects

Nine well trained male divers were enlisted for this study. They were 37 ± 6 years old, 78 ± 7 kg in weight and 176 ± 6 cm tall. All divers were healthy and non-smokers. None of them had previous history of cardiovascular, pulmonary, or neurological diseases, or was taking any medication at the time when the study was carried out. Their

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Table 1
Mean values of cardiovascular variables recorded during steady state exercise before apnoeas (Pre-apnoea), during the steady state phase (only for apnoeas in oxygen), and at the beginning and at the end of the last unsteady phase (mean value over 10 beats). Punctual value of the beginning of the first unsteady phase and in correspondence of the minimum of systolic blood pressure (MSBP) during the same phase. Data are presented as means and standard deviations both for apnoeas performed in air and in pure oxygen. SBP, systolic blood pressure; DBP, diastolic blood pressure; f_H, heart rate; Q_S, stroke volume; $\dot{Q}$, cardiac output; TPR, total peripheral resistances.

		Pre-apnoea	First unsteady phase		Steady state phase	Last unsteady phase	
		mean value	beginning	MSBP	mean value	beginning	end
SBP	air	162 ± 32$^{\#}$	176 ± 39$^{\#}$	102 ± 24	–	173 ± 40$^{\#}$	215 ± 49$^{\#}$
(mmHg)	O_2	166 ± 22$^{\#\S}$	166 ± 43$^{\#\S}$	111 ± 29	185 ± 29$^{\#}$	194 ± 31$^{\#}$	214 ± 36$^{\#}$
DBP	air	74 ± 12	76 ± 11$^{\#}$	51 ± 9	–	82 ± 15$^{\#}$	96 ± 19$^{\#\&}$
(mmHg)	O_2	78 ± 7$^{\#\S}$	81 ± 13$^{\#\S}$	59 ± 13	87 ± 10$^{\#}$	91 ± 11$^{\#}$	104 ± 12$^{\#}$
f_H	air	99 ± 13$^{\&}$	105 ± 14§	109 ± 14§	–	107 ± 15§	76 ± 25
(bpm)	O_2	94 ± 13	102 ± 18§	104 ± 14§	93 ± 16	90 ± 16	78 ± 17
Q_S	air	114 ± 18	83 ± 23*	70 ± 22*	–	78 ± 12*	104 ± 15$^{\#}$
(ml)	O_2	114 ± 18	73 ± 30*	70 ± 16*	91 ± 16	94 ± 17	99 ± 18
$\dot{Q}$	air	11.2 ± 2.3$^{\&}$	8.6 ± 2.4	7.4 ± 1.7*	–	8.3 ± 1.8	7.8 ± 2.4*
($l\,min^{-1}$)	O_2	10.6 ± 2.1	8.0 ± 1.9	7.2 ± 1.5*	8.5 ± 2.2	8.5 ± 2.2	7.6 ± 1.9*
TPR	air	9.2 ± 2.3$^{\S\&}$	12.6 ± 3.5	8.8 ± 1.8$^{\S\&}$	–	13.2 ± 3.5	18.5 ± 7.0
($mmHg\,min\,l^{-1}$)	O_2	10.1 ± 1.8§	11.0 ± 6.9§	10.0 ± 2.1§	14.1 ± 3.1	14.9 ± 4.2	19.1 ± 5.6

*: $p < 0.05$ vs pre-apnoea mean value in the same condition.
$^{\#}$: $p < 0.05$ vs MSBP value during the first unsteady phase in the same condition.
§: $p < 0.05$ vs the end of the last unsteady phase in the same condition.
$^{\&}$: $p < 0.05$ vs the same value in apnoeas performed in pure oxygen.

predicted total lung capacity was 7.0 ± 0.4 l (Stocks and Quanjer, 1995). All gave their informed consent after having received a detailed description of the methods and experimental procedures of the study. The study was approved by the local ethical committee and conformed to the Declaration of Helsinki.

2.2. Experimental procedure

Experiments were carried out in Lindos, Greece, in an air-conditioned room at 23–24 °C, with relative humidity between 60 and 65%. Subjects came to the laboratory on two occasions: one for the tests in air and the other for the tests in oxygen. Air and oxygen were administered in random order. 5 subjects begun with the test in oxygen and 4 subjects with the test in air. At least 2 days separated the 2 tests. Oxygen was administered from a high-pressure tank, via a Douglas bag that was used as pressure buffer. Upon arrival in the laboratory and after instrumentation and familiarization with procedures, the subject was asked to sit on a cycle-ergometer. In oxygen experiments, after connection to the oxygen delivery system, ten minutes were then allowed for alveolar gas equilibration.

The experimental protocol was as follows: the subject performed 40 W exercise at 60 revolutions per minute; after 5 min, which were necessary to achieve steady state conditions, pre-apnoea control values were collected (PRE); then, the subject was asked to perform one maximal apnoea while still exercising. Both in air and in pure oxygen, the subject's pre-dive routine consisted of a couple of deep respiratory acts and was undertaken before breath-holding. A deep inspiration preceded the apnoeas, so that the lung volume at which the apnoeas started was close to the subject's total lung capacity.

2.3. Measurements and data treatment

Arterial blood pressure profiles (Portapres®, TNO-TPD, Amsterdam, The Netherlands) were continuously recorded throughout the experiments. Peripheral blood O_2 saturation (SpO_2) was continuously monitored by infrared spectroscopy (OXY100E module, BIOPAC® System Inc., Goleta, CA, USA) at an earlobe. f_H was continuously measured on a beat-by-beat basis by electrocardiography (ECG100C module, BIOPAC® System Inc., Goleta, CA, USA). The signals were sampled at 100 Hz by using a 16-bit A/D converter (MP150 system, BIOPAC® System Inc., Goleta, CA, USA) and stored on a personal computer for subsequent off-line analysis. The breath-by-breath recording of inspiratory and expiratory flows was performed by an ultrasonic flowmeter (Spiroson®, ECO MEDICS AG, Duernten, Switzerland) calibrated with a three-litre syringe.

Duration of apnoea was obtained from the analysis of respiratory flows. Arterial pressure profiles were analysed off-line, to obtain beat-by-beat values of systolic (SBP), diastolic (DBP), and mean (MBP) arterial pressure using the Beatscope® software (FMS, Amsterdam, The Netherlands). Single-beat Q_S was determined by means of the Modelflow method (Wesseling et al., 1993), applied off-line to the pulse pressure profiles, again using the Beatscope® software package. Beat-by-beat cardiac output ($\dot{Q}$) was then computed as the product of single-beat Q_S times the corresponding single-beat f_H. Total peripheral resistances (TPR) were calculated as the ratio between MAP and $\dot{Q}$.

An automated procedure implemented under MATLAB (version 7.6.0.324, MathWorks®, Natick, MA, USA) was used to identify the three phases of apnoea (Fagoni et al., 2017, 2015; Sivieri et al., 2015) by means of linear regression analysis, allowing the detection of changes in slope between successive phases.

2.4. Statistical analysis

Data are presented as mean and standard deviation (SD). Paired Student T-test was used to compare apnoeas performed in air and in pure oxygen; one-way ANOVA was used to compare cardiovascular data during the time course of apnoeas and Tukey test was used as post-hoc test to isolate the differences when necessary. Differences were considered significant when $p < 0.05$, otherwise they were considered non-significant (NS). The statistical software SPSS (Chicago, USA) was used for this aim.

3. Results

Means and standard deviations of all the cardiovascular variables recorded before and during apnoeas are reported in Table 1. In PRE, they differed between air and oxygen conditions for $\dot{Q}$, that was lower (−5.0 ± 3.2%) in oxygen than in air, due to a lower f_H (−5.3 ± 5.7%) coupled with an unchanged Q_S. Basal SpO_2 was 98.7 ± 1.2% in air and 100% in pure oxygen. Apnoeas lasted 45.0 ± 16.9 s in air and 77.0 ± 28.9 s in pure oxygen ($p < 0.05$).

Examples of the time courses of SBP, DBP and f_H during apnoea

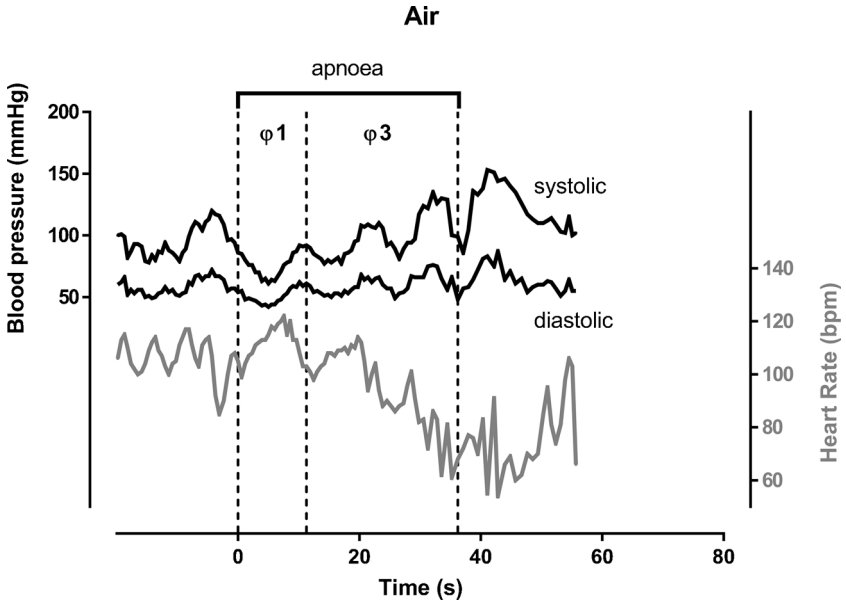

Fig. 1. Time course of heart rate, systolic and diastolic blood pressure from a maximal dynamic apnoea in air. φ1: first unsteady state phase; φ3: last unsteady state phase.

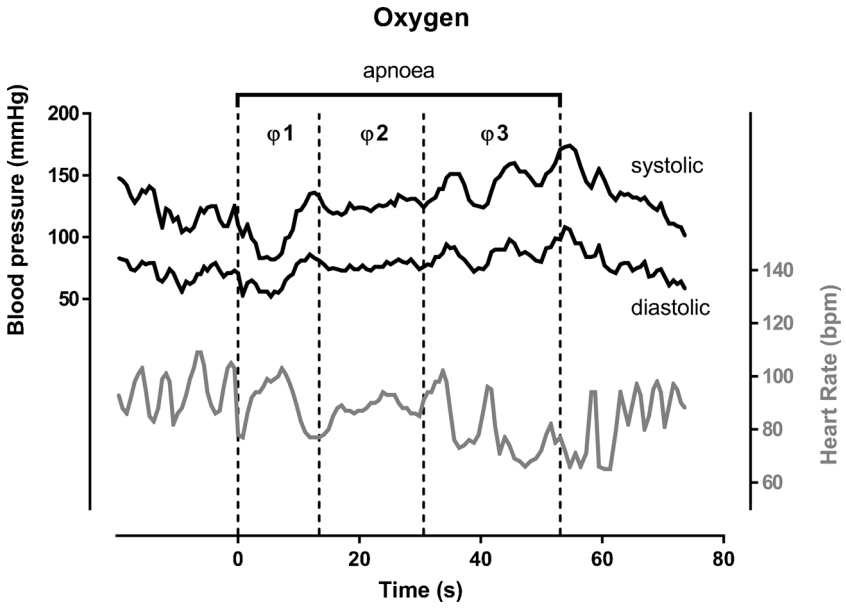

Fig. 2. Time course of heart rate, systolic and diastolic blood pressure from a maximal dynamic apnoea in pure oxygen. φ1: first unsteady state phase; φ2: steady state phase; φ3: last unsteady state phase.

from a representative subject in air and in pure oxygen are shown, respectively, in Figs. 1 and 2. The trend over time of the cardiovascular variables allowed the partition in different phases, the first characterised by a sudden fall in SBP to a minimum value (MSBP) with a subsequent recovery. This phase was identified as φ1 and lasted 11.5 ± 1.4 s in air and 11.2 ± 1.3 s in pure oxygen (NS). At the very first beat of apnoea, the observed values did not differ from PRE in both conditions, except for Q_S which was lower both in air (−28 ± 16%) and in oxygen (−30 ± 12%).

In apnoeas performed in air, no steady state phase could be identified after φ1. Conversely, in apnoeas performed in pure oxygen, φ1 was followed by a clearly identified steady state φ2, with a mean duration of 28.5 ± 5.4 s.

At the end of φ2 in apnoeas performed in pure oxygen, a final phase characterised by a continuous increase in SBP and in decrease in f_H was observed (φ3). This phase lasted 37.4 ± 24.5 s. In air, a similar pattern was observed at the end of φ1, lasting 33.5 ± 17.1 s.

At the end of apnoeas performed in air, SpO_2 attained a minimum of 95.5 ± 1.9% ($p < 0.05$ with respect to PRE) while in apnoeas performed in pure oxygen SpO_2 remained equal to 100%.

4. Discussion

To our knowledge, this study is the first beat-by-beat analysis of the time course of cardiovascular variables during exercising apnoeas performed in pure oxygen. The main finding of our investigation was the appearance of a steady state phase, *i.e.* φ2, in these breath-holds, in support of the tested hypothesis (Fagoni et al., 2015; Sivieri et al., 2015).

Sivieri et al. (2015) subdivided the cardiovascular responses of

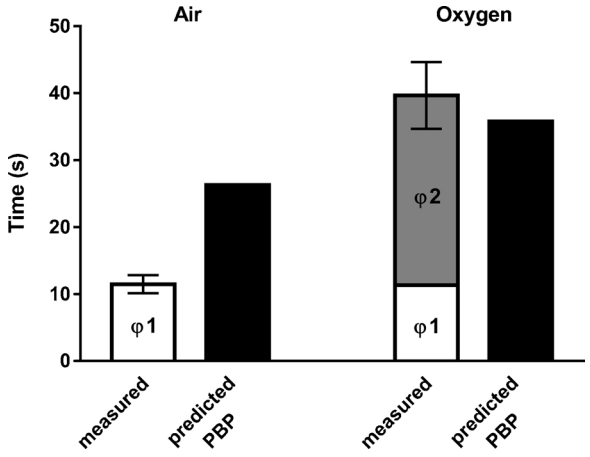

Fig. 3. Means and standard deviation of measured durations of φ1 (in white) and φ2 (in grey) of breath-holds in air and in pure oxygen are represented. Predicted times to physiological breaking point (in black) obtained with Lin's model (1974), see text for details, are also shown. φ1 and φ2: first unsteady state phase and steady state phase, respectively, of the cardiovascular responses of measured apnoeas; PBP: physiological breaking point.

exercising apnoeas in ambient air in two distinct phases. Our study suggests that these two phases can be identified with φ1 and φ3. We can, thus, speculate that, in exercising apnoeas performed in air, the trigger of the transition from φ2 to φ3 might have occurred before the end of φ1. Conversely, in pure oxygen, φ3 started after the end of φ1, so that a clear steady-state φ2 could be identified. Moreover, the appearance of φ2 in exercising apnoeas in pure oxygen is in line with the increase in φ2 duration in resting oxygen apnoeas (Fagoni et al., 2015).

The duration of φ1 was the same in the two tested conditions. In previous papers, no differences in φ1 duration were found between rest and exercise in air (Sivieri et al., 2015) and between air and oxygen in resting apnoeas (Fagoni et al., 2015). This justifies the assumption that the duration of φ1 is invariant and independent of the metabolic rate and of the amount of oxygen stored in the body. The fall of SBP and its subsequent recovery and the specular f_H time course, was similar in the two conditions, as in previous studies (Fagoni et al., 2017, 2015; Sivieri et al., 2015). The observed SAP fall agrees with the hypothesis that φ1 is a consequence of the deep inspiratory manoeuvre preceding the apnoea, in which case the increase in f_H would reflect a baroreflex attempt at compensating for the fall in SAP (Adami et al., 2013; Fagoni et al., 2015; Sivieri et al., 2015; Taboni et al., 2018). If this hypothesis is correct, then the fall in SAP would occur along the steep part of a baroreflex function curve, which may be in contrast with Costalat's model (Costalat et al., 2017, 2015) since the SAP patterns at the beginning of the present apnoeas would not be compatible with the exponential drop in f_H that those authors assumed.

On the other extreme, the model of Costalat et al. (2015), which was also applied to exercising face-immersed breath-holds (Costalat et al., 2017), implies that the time course of f_H is characterised by a final phase of linear decrease that is very similar with the f_H time course of φ3 of our apnoeas. The lack of this final drop in f_H during exercising apnoeas in non-divers (Costalat et al., 2017) is in line with the observation that in breath-holds of shorter durations φ3 cannot be identified (Perini et al., 2008). Nevertheless, it was hypothesised that the triggering of this final phase, the so-called oxygen conserving point, was linked to a given SpO_2 (~95%) in his tested settings, *i.e.* maximal resting apnoeas performed in air in dry-body and in immersed-body conditions (Costalat et al., 2015), and in face-immersed exercising apnoeas (Costalat et al., 2017). This is in contrast with the observation that also in apnoeas performed in pure oxygen a final linear decrease in f_H values can be identified while the SpO_2 remained unchanged at 100%. This finding suggests that hypoxia is not the only explanation of the elicitation of φ3.

Alternatively, the start of φ3 may be associated with the onset of involuntary respiratory muscle activity, generated by a ventilatory drive that overcomes the voluntary inhibition of the respiratory muscles (Agostoni, 1963). This ventilatory drive is linked to precise alveolar gas compositions (Agostoni, 1963; Fowler, 1954), which are attained more rapidly when apnoeas are performed at exercise. In hyperoxia, the conditions determining the onset of φ3 are attained in a time that is longer than in normoxia, but shorter than what we could predict on the basis of the incurring oxygen stores. The oxygen stores increase 5 times indeed, while the onset of φ3, if we admit that in air it may correspond to the end of φ1, increases only 3.5 times. In oxygen apnoeas, the conditions at the end of φ2 cannot be the same as in air, since SpO_2 does never go below 100% both at rest (Fagoni et al., 2015) and at exercise. So, no hypoxic stimulation participates in determining the onset of φ3: if it is indeed the ventilatory drive which generates the onset of φ3, we speculate that it should be due to a hypercapnic stimulus.

This latter speculation is coherent with the conjecture (Fagoni et al., 2015; Perini et al., 2010, 2008; Sivieri et al., 2015) that the onset of φ3 may correspond to the physiological breaking point of apnoea as defined by Lin et al. (1974). These authors proposed also a linear relationship between breath-hold time and the reciprocal of oxygen consumption in order to predict the time of the first diaphragmatic contraction and the maximal breath-hold time. In the impossibility of obtaining direct measures of partial pressure of CO_2 on that occasion in Rhodes, we fit our data into Lin's model. If we admit an increase in oxygen consumption of 11.19 ml O_2 min^{-1} W^{-1} when pedalling at 60 revolutions per minute (Bonjour et al., 2010; Ferretti et al., 2017; Francescato et al., 1995), we would thus be able to obtain indirect predictions of the time of the first diaphragmatic contraction in air and in pure oxygen. These predictions are illustrated in Fig. 3. When exercising apnoeas are performed in pure in oxygen, the physiological breaking point would be at 35.8 s. In our study, the time necessary to reach the beginning of φ3 in apnoeas performed in pure oxygen was 37.6 ± 8.0 s. This similarity agrees with the hypothesis that the transition from φ2 to φ3 occurs at the physiological breaking point.

Nevertheless, things are not so straightforward for exercising apnoeas in air. In fact, Lin's model would provide a time to attain the physiological breaking point of 26.3 s for apnoeas in air. However, no apparent steady phase was detected in our experimental breath-holds, as in a previous study (Sivieri et al., 2015). If we admit, as pointed out above, that the two phases of exercise apnoeas in air correspond to φ1 and φ3, then the beginning of φ3 would occur at latest at the end of φ1, for which a duration of 11.5 ± 1.4 s was found, which is less than one half of the time to the physiological breaking point provided by Lin's model. This apparent discrepancy may have a methodological origin. On one side, Lin et al. (1974) identified the physiological breaking point by the analysis of intraesophageal pressure oscillations, so they might have missed the first diaphragmatic contraction during exercise; on the other side, the φ2 duration in exercise apnoeas in air may be so short to be undetectable as a φ2–φ3 transition. This means that, if we wish to identify a more precise link between the physiological breaking point and the triggering of φ3 during exercise apnoeas in air, a study implying a direct measurement of involuntary ventilatory activity and alveolar gas compositions, beside the cardiovascular time courses, becomes mandatory.

4.1. Limitations of the study

This study has nevertheless some limitations. The most important, in view of the speculations proposed in the discussion, appears to be the absence of a direct determination of the physiological breaking point, which would have clarified the relationships between the cardiovascular responses and the ventilatory drive. The direct measurement of the involuntary ventilatory activity is, however, an invasive procedure

(Agostoni et al., 1960), that is hard to perform on exercising humans. A determination of alveolar gas composition before and after apnoeas would have reduced speculation uncertainty, because Lin's formulae for the prediction of the time to the first diaphragmatic contraction may be affected by the alveolar gas composition at the beginning of apnoea. However, no specific gas analyser was available on the spot.

Moreover, we note that the subjects of this study were trained divers, so the study of a control group of untrained divers would have been useful. However, Perini et al. (2008) demonstrated that untrained subjects, who cannot prolong their breath-holds in air for longer than 3 min at rest, must interrupt their apnoeas before a clear appearance of φ3. So, no transition between φ2 and φ3 could be identified in them. This limited the study to a group of well-trained divers. As a consequence, we cannot exclude that the cardiovascular responses to exercising apnoeas in air and in pure oxygen obtained in this study are affected by a selection bias or by some form of adaptation.

5. Conclusions

The results support the tested hypothesis since in exercising apnoeas performed after breathing pure oxygen a clearly identifiable and measurable φ2 appears. The two phases, in which the cardiovascular variables' time course of exercise apnoeas in air could be divided, might be representative of φ1 and φ3 of oxygen breath-holds. Thus, the φ2–φ3 transition might occur before the end of φ1 when exercising apnoeas are performed in air and after the end of φ1 when they are performed in pure oxygen.

Declarations of interest

None.

Acknowledgments

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