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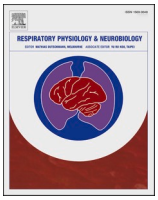

Changes in hormones after apneic hypoxia/hypercapnia - An investigation in voluntary apnea divers

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ABSTRACT

Background: Prolonged apnea is characterized by hypoxia/hypercapnia. Hypoxia can be associated with hormonal dysfunction. We raised the question as to whether steroid hormonal and gonadotropin levels could be influenced by short-term hypoxia/hypercapnia in a model of dry apnea in trained apnea divers.
Methods: Adrenal, sex steroid and pituitary hormones were measured in ten trained voluntary apnea divers before, immediately after, 0.5 h and 4 h after a maximal breath-hold. Apnea was carried out under dry conditions.
Results: Corticosterone, progesterone, cortisol, 17−OH-progesterone, dehydroepiandrosterone and androstenedione showed a significant continuous increase with a maximum at 0.5 h after apnea, followed by a decrease back to or below baseline at 4 h after apnea. Testosterone, estradiol, cortisone and dihydrotestosterone showed a decrease 4 h after apnea. Dehydroepiandrosteronesulfate, luteinizing hormone (LH) and follicle stimulating hormone (FSH) showed no significant changes.
Conclusion: Even a single apnea resulted in two different patterns of hormone response to apnea, with increased adrenal and reduced sex steroid levels, while LH/FSH showed no clear kinetic reaction. Apnea divers might be a suitable clinical model for hypoxic disease.

1. Introduction

Apnea diving or breath-hold diving is the oldest known type of diving (Levett and Millar, 2008). In recent years, recreational as well as competitive apnea diving has become very popular (Fernández et al., 2019). Prolonged apnea is characterized by extended hypoxia and hypercapnia. Physiological compensatory mechanisms (the so-called diving response) help to maintain adequate oxygen supply to the brain (Dujic and Breskovic, 2012; Eichhorn et al., 2015, 2018). Hypoxia seems to trigger the release of endothelial microparticles (EMPs), which are associated with endothelial dysfunction (Deng et al., 2017; Vince et al., 2009). Even in healthy divers, one single episode of hypercapnia and hypoxia leads to endothelial dysfunction (Eichhorn et al., 2017a, 2017b).

While physiological and pathophysiological processes are not yet fully understood, safety concerns are raised when performing apnea diving. Apnea divers are exposed to specific environmental and physiological stressors (Elia et al., 2021). Elia et al. further state that, while considering increasing numbers of apnea divers and growing popularity, awareness regarding possible health implications should be increased (Elia et al., 2021). Studies investigated, e.g., the impact of apneic diving on splenic volume (Baković et al., 2003), cardiovascular burden (Eichhorn et al., 2018), blood cells (Dolscheid-Pommerich et al., 2020) and skeletal muscle (Kjeld et al., 2018) as well as impacts on hormones, such as erythropoietin (Kjeld et al., 2015).

To our knowledge, no study has been performed to date to investigate whether hypoxia in a model of trained apnea divers under dry apnea conditions can be associated with adrenal, sex steroid and pituitary hormonal dysfunction. Therefore, we raised the question as to whether short-term hypoxia/hypercapnia affects adrenal, sex steroid and pituitary hormone levels. While studies performed in humans and rats have also focused on hypoxemia, heart ischemic markers, cortisol and clinical parameters, no investigation of steroid hormones using state of the art chromatography-tandem mass spectrometry analysis (LC–MS/

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Table 1
Physical characteristics of apnea divers.

Subject No.	Age [years]	Total apnea time [s]	SpO_2 at start of apnea	Minimal SpO_2	Heart frequency at onset of apnea [bpm]	Heart frequency at end of apnea [bpm]	Sex
1	52	305	100	59	115	46	male
2	37	309	99	49	80	49	male
3	47	244	99	86	99	57	male
4	30	587	99	67	80	77	male
5	51	326	100	67	85	46	male
6	25	374	100	68	95	48	male
7	30	168	100	91	83	51	male
8	47	338	100	73	79	32	male
9	54	365	100	75	70	50	female
10	39	278	100	82	77	56	female
Mean	41	329	99.7	71.7	86.3	51.2	
SD	9.90	103.29	0.46	11.95	12.48	10.78	

MS) have been performed in apnea divers to date (Marlinge et al., 2019). In contrast to steroid hormone values obtained with immunoassays, no cross-reactions with other metabolites are observed. Additionally, LC–MS/MS analysis has the advantage of analyzing multiple steroids within one single run with low sample volumes.

Therefore, we investigated whether an acute apneic stress situation affects steroid and gonadotropin hormone concentrations in trained apnea divers. Aim of the present study is to provide further insight into steroid hormone changes after apneic hypoxia/hypercapnia.

2. Materials and methods

2.1. Ethics and patient collective

Trial registration number: DRKS00021448. This single-center prospective study received approval (373/13) from the local ethics committee (chairman K. Racké, MD, PhD, professor, University Clinics Bonn, Germany) in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all healthy adult participants. A prerequisite for participation was an experience of 270 s as minimum apnea time to ensure that the divers were adequately trained athletes able to reduce their SpO_2 levels by voluntary apnea. Heart rate and peripheral oxygen saturation (SpO_2) were measured by a patient monitoring device (Expression MR400, Invivo, Gainsville, FL, USA).

Ten divers (eight males, two females with a mean age of 41 years (± 10 years standard deviation (SD)) were included (for physical details see Table 1). Apnea was carried out by each participant in the morning at a horizontal position under dry conditions. We obtained 7.5 mL venous blood through a permanent venous catheter before apnea, immediately after apnea, 0.5 h and 4 h later.

Table 1 shows age, total apnea time, SpO_2 (start of apnea and minimal values), heart frequency (at onset and end of apnea) and sex of apnea divers, including mean values and standard deviations.

2.2. Laboratory analysis

After sampling, plasma was immediately stored at −80 °C and measurements were performed in batches. Levels of cortisol, cortisone, corticosterone, androstenedione, dehydroepiandrosterone/sulfate (DHEA, DHEAS), testosterone, dihydrotestosterone (DHT), estradiol, 17−OH-progesterone (17−OHP) and progesterone were measured with chromatography-tandem mass spectrometry analysis (LC–MS/MS) by MassChrom® in serum/plasma (Chromsystems, Graefelfing, Germany) with Xevo® TQ-S mass spectrometer (Waters, Eschborn, Germany). Luteinizing hormone (LH) and follicle stimulating hormone (FSH) were analyzed by immunoassays (Vista1500™, Siemens Healthineers, Eschborn, Germany).

2.3. Statistics

Statistical analyses were performed using GraphPad® Prism 8.2 (GraphPad Software, La Jolla/CA, USA), MedCalc® for Windows, Version 11.0.0.0 (MedCalc Software, Ostend, Belgium) and SAS® (SAS Institute Inc., Cary, NC, USA. Version 9.4.). Variables are described as mean values and standard deviations. Boxplots depict the value distributions of the steroid and gonadotropin hormones for the different time points. Time dependency of steroid hormonal and gonadotropin levels was analyzed in a mixed linear model. Baseline differences were tested separately as differences from zero (one sample t-test). Tests were performed for the whole collective as well as only for the male participants.

Table 2
Mean values, standard deviations and *p*-values of steroid hormones and gonadotropins at different time points: baseline concentrations, immediately post apnea, 0.5 h and 4 h after apnea.

Mean [SD]	Baseline concentration	Post apnea	30min post apnea	4 h post apnea	*p*-value whole collective	*p*-value males only
Androstenedione nmol/l	2.3 [1.2]	3.1 [1.3]	3.2 [1.3]	1.6 [0.3]	**<0.0001**	**<0.0001**
Corticosterone nmol/l	7.4 [10.3]	18.8 [21.3]	30.3 [19.3]	3.9 [3.7]	**<0.0001**	**0.0004**
Cortisol nmol/l	275.7 [122.2]	364.3 [125.2]	438.8 [94.8]	195.8 [89.4]	**<0.0001**	**<0.0001**
Cortisone nmol/l	55.7 [11.9]	55.5 [13.8]	56.2 [10.9]	36.9 [8.7]	**<0.0001**	**<0.0001**
DHEA µmol/l	0.03 [0.02]	0.04 [0.02]	0.04 [0.02]	0.02 [0.01]	**<0.0001**	**<0.0001**
DHEAS µmol/l	5.4 [2.2]	5.3 [2.3]	5.1 [2.1]	5.3 [2.2]	0.519	0.6145
DHT pmol/l	1.4 [0.6]	1.5 [0.7]	1.5 [0.5]	1.2 [0.4]	**0.015**	**<0.0001**
Estradiol nmol/l	0.4 [0.6]	0.4 [0.5]	0.4 [0.5]	0.3 [0.6]	0.585	0.4968
FSH IU/l	7.1 [11.3]	6.6 [10.1]	6.5 [10.1]	6.9 [11.0]	0.244	0.7108
LH IU/l	5.0 [8.0]	4.8[6.9]	5.1[6.7]	5.2 [7.2]	0.810	0.4120
Progesterone nmol/l	0.2 [0.1]	0.3 [0.2]	0.4 [0.2]	0.2 [0.1]	**<0.0001**	**0.0005**
Testosterone nmol/l	14.2 [9.2]	14.2 [9.9]	11.4 [8.5]	10.7 [7.4]	**<0.0001**	**<0.0001**
17-OHP nmol/l	2.0 [1.2]	2.5 [1.4]	2.4[1.1]	1.4 [1.0]	**0.0001**	**0.0003**

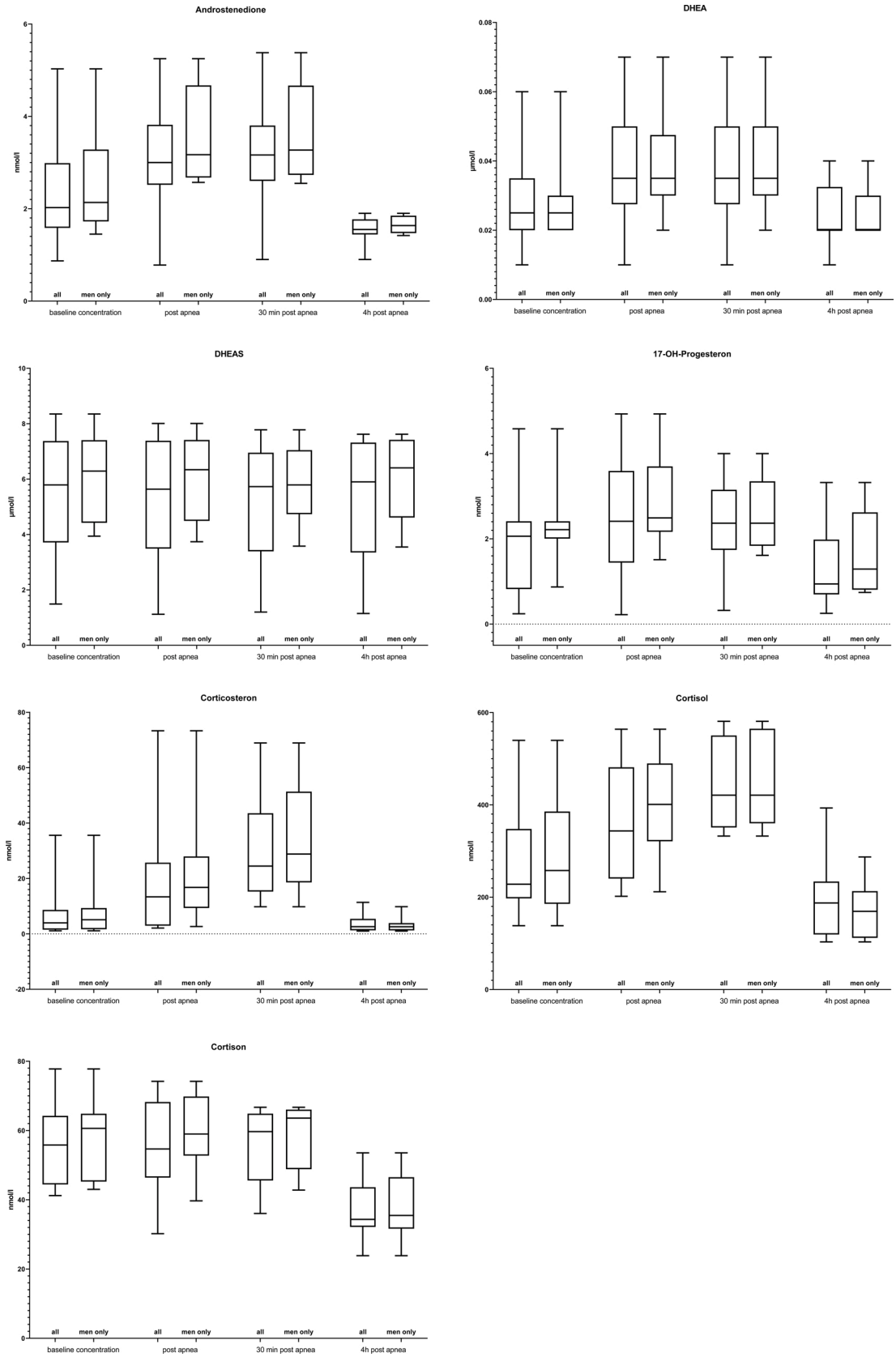

Fig. 1. Concentration changes of adrenal steroids.
Displayed are value distributions of the whole collective (all) as well as only of the male participants for the adrenal steroids androstenedione, corticosterone, cortisol, DHEA, 17−OHP, cortisone and DHEAS. Bars represent the median, while box plots show interquartile range and whiskers.
Dehydroepiandrosterone (DHEA), 17−OH-progesterone (17−OHP), Dehydroepiandrosteronesulfate (DHEAS).
*One value did not meet the required LC–MS/MS signal to noise ratios and was excluded from consideration.

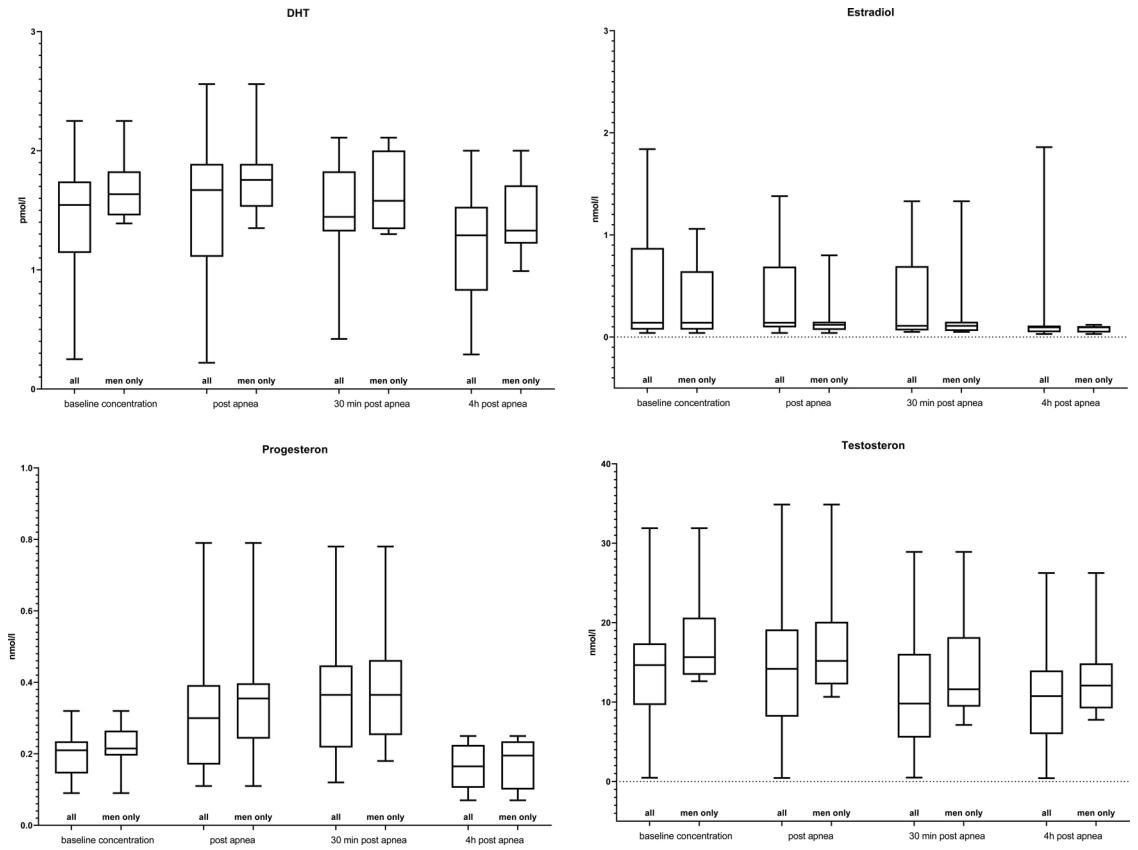

Fig. 2. Concentration changes of gonadal steroids.
Displayed are value distributions of the whole collective (all) as well as only the male participants for the gonadal steroids progesterone, testosterone, estradiol and DHT. Bars represent the median, while box plots show interquartile range and whiskers.
Dihydrotestosterone (DHT).
*Two values did not meet the required LC–MS/MS signal to noise ratios and were excluded from consideration.

3. Results

Mean values and standard deviations of steroid hormones and gonadotropins were calculated before apnea, immediately, 0.5 h and 4 h after apnea and are presented in Table 2.

Table 2 shows median values, standard deviations (SD) and *p*-values for overall significance for the whole collective as well as only the male participants for cortisol, cortisone, corticosterone, androstenedione, dehydroepiandrosterone/sulfate (DHEA, DHEAS), testosterone, dihydrotestosterone (DHT), estradiol, 17−OH-progesterone (17−OHP), progesterone, luteinizing hormone (LH) and follicle stimulating hormone (FSH).

Whisker and boxplots show the value distributions of steroid and gonadotropin hormones for the different time points. Androstenedione, corticosterone, cortisol, DHEA and 17−OHP showed a continuous increase with a maximum 0.5 h after apnea followed by a decrease (in corticosterone) back to or below baseline 4 h after apnea. Cortisone showed decreased levels 4 h after apnea and DHEAS showed no clear kinetic reaction. Kinetic profiles of adrenal steroids are shown in Fig. 1.

Progesterone showed a continuous increase with a maximum 0.5 h after apnea followed by a decrease below baseline 4 h after apnea. Testosterone, estradiol and DHT showed decreased levels 4 h after apnea. Kinetic profiles of gonadal steroids are shown in Fig. 2 [Fig. 2].

Pituitary hormones LH and FSH showed no clear kinetic reaction [Fig. 3].

Differences between the time intervals are presented in Table 3.

Table 3 shows the differences between the time intervals for cortisol, cortisone, corticosterone, androstenedione, dehydroepiandrosterone/sulfate (DHEA, DHEAS), testosterone, dihydrotestosterone (DHT), estradiol, 17−OH-progesterone (17−OHP), progesterone, luteinizing hormone (LH) and follicle stimulating hormone (FSH).

T1 = baseline concentration, T2 = post apnea, T3 = 0.5 h post apnea, T4 = 4 h after apnea

4. Discussion

We investigated whether short-term hypoxia/hypercapnia under dry apnea conditions affects hormonal levels in trained apnea divers. Our research identified two different patterns of hormone response to apnea with increased adrenal and reduced sex steroid levels.

The stress markers cortisol and corticosterone markedly increased after apnea. Factors like cold or hyperbaric exposure might trigger hormonal changes in apnea divers. While comparing SCUBA divers, apneic dives and dry static apnea, Marlinge et al. observed that hypoxia plays a major role in releasing stress hormones and cardiac injury markers, while other triggers only play a minor role in apnea divers (Marlinge et al., 2019). This is in line with similar findings from high altitude studies, where acute normobaric hypoxia (~11.0 % FiO_2) increased cortisol levels in participants while testing single exposures simulating high altitude (Cooke et al., 2018). Although pathophysiological responses at a high altitude differ from those found after a single apnea event, it is of interest that elevated concentrations of corticosterone were also found in rats exposed to chronic intermittent hypoxia (Hwang et al., 2017).

In our study, a model of dry apnea was performed to exclude disruptive effects and to allow closer inspection of the kinetical profile of stress hormones affected by hypoxia and hypercapnia. A single stimulus of a maximum apnea resulted in trained apnea divers in increased levels

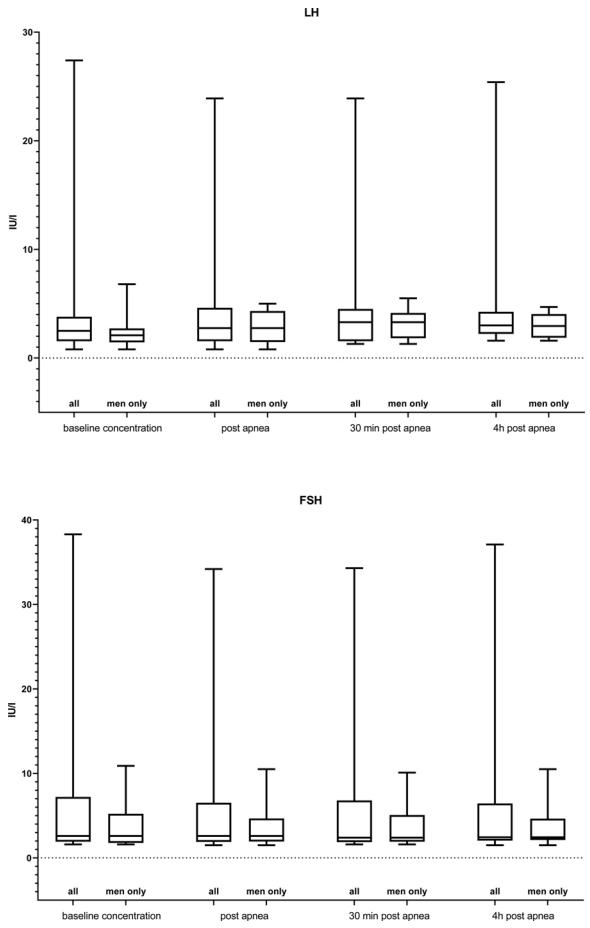

Fig. 3. Concentration changes of pituitary hormones.
Displayed are value distributions of the whole collective (all) and men only for the pituitary hormones LH and FSH. Bars represent the median while box plots show interquartile range and whiskers.
Follicle stimulating hormone (FSH) and luteinizing hormone (LH).

of cortisol and corticosterone within 30 min. An accumulative effect was also seen in a study by Kon et al., where participants performed resistance exercises while breathing hypoxic air (13 % FiO_2), leading to a SpO_2 of 84.1 ± 0.6 %. Compared to controls, cortisol levels were significantly elevated in the post-exercise period. No difference was seen at baseline and 60 min after exercise, whereas levels increased in the time period of 15 and 30 min after the exercise. The authors speculated that the acute cortisol response was caused by hypoxia (Kon et al., 2010). Cortisone, as the inactive metabolite of cortisol, showed no significant elevation after this single apnea stimulus under dry conditions. The cortisone concentration is physiologically lower than cortisol and is associated with chronic stress (Friedenreich et al., 2019).

In naturally cycling women, progesterone and cortisol increased during physical stress (Herrera et al., 2016). In males, in response to acute metabolic stress, not only levels of cortisol, but also levels of adrenal progesterone were found to be increased (Elman and Breier, 1997; Herrera et al., 2016). These findings are in line with our observation, namely that even a single apnea event under dry conditions resulted in concordant kinetic changes of progesterone and cortisol in our collective. Four hours after the acute stress event of apnea, progesterone and cortisol levels returned to baseline or to even lower values. Repeat measurements are needed to confirm findings focusing on antioxidant functions.

Although the causality remains unclear, our data show that a single apnea event under dry conditions resulted in reduced levels of the concentrations of the sex steroids testosterone, estradiol and DHT four hours after apnea in trained apnea divers. Hypoxia seems to be one of the key modulators for changes in steroids and gonadotropins. While in our study, CO_2 levels were not measured, the role of hypercapnia as an important stimulus for adrenal hormones should be considered. In a previous study, we found an increase of end-expiratory CO_2 levels from 29 ± 4 mmHg to 49 ± 6 mmHg and an increase in systolic blood pressure (measured by NIBP) from 135 ± 13–185 ± 25 mmHg (Eichhorn et al., 2017a, 2017b). From animal studies, it is known that inhalation of CO_2 leads to a release of adrenal glucocorticoids in calves (Bloom et al., 1977). Koelsch et al. (2016) administered a CO_2 stress test to 142 participants (inhalation of 35 % CO_2), who presented changes in the hypothalamic–pituitary–adrenal (HPA) axis hormones, in sympathetic endocrine activity, inflammation, and in metabolic function. Interestingly, we found increased norepinephrine and epinephrine levels after a single maximal breath-hold and correlated them to bradycardia (Eichhorn et al., 2017a, 2017b). Apnea diving might substantially burden the cardiovascular system (Eichhorn et al., 2018).

Hypercapnia seems to play an important role in endogenous stress synthesis and resulting hormonal changes. Our study indicates that even a single short maximal breath-hold triggers the hormonal axis and leads to significant changes in trained apnea divers.

No significant changes were found for LH, FSH and DHEAS. High altitude studies have shown that hypoxia caused adverse, but reversible effects on gonadotropins, whereby these effects were reversible six months after exposure (He et al., 2015). Therefore, future studies should investigate our findings in reproducible apnea conditions. Short-term effects were reported in hypoxia mountain training exercises. However, the applied investigation methods are not comparable to the current state of the art LCMS-MS techniques (Friedl et al., 1988).

Table 3
Differences between the time intervals of steroid hormones and gonadotropins.

	Whole collective			Male participants only		
	p-value T2 vs. T1	p-value T3 vs. T1	p-value T4 vs. T1	p-value T2 vs. T1	p-value T3 vs. T1	p-value T4 vs. T1
Androstenedione	**0.0143**	**0.0069**	**0.0138**	**0.0109**	**0.0072**	**0.0107**
Corticosterone	0.0506	**0.0003**	0.5353	**0.0389**	**0.0007**	0.4139
Cortisol	0.0587	**0.0010**	0.0635	**0.0225**	**0.0014**	**0.0088**
Cortisone	0.9681	0.8922	**<0.0001**	0.6739	0.8185	**<0.0001**
DHEA	**0.0024**	**0.0008**	0.0714	**0.0008**	**0.0003**	0.0808
DHEAS	0.6101	0.1459	0.5427	0.8998	0.2385	0.8059
DHT	0.3744	0.3881	**0.0388**	0.0691	0.5157	**0.0003**
Estradiol	0.7388	0.6370	0.1873	0.5358	0.8030	0.1553
LH	0.6684	0.8390	0.6043	0.4526	0.1141	0.2300
FSH	0.0969	0.0851	0.4849	0.3860	0.2809	0.4471
Progesterone	**0.0136**	**0.0008**	0.4105	**0.0102**	**0.0022**	0.3919
Testosterone	0.9798	**0.0029**	**0.0003**	0.9778	**0.0012**	**0.0001**
17-OHP	0.0550	0.0951	**0.0257**	**0.0317**	0.3424	**0.0070**

4.1. Limitations of the study

Other studies in apnea diving had a comparable collective size (Eftedal et al., 2016). The significance level of $p < 0.05$ should be considered to be descriptive and explorative. Therefore, p-values were not corrected for multiple testing. A single apnea may not reflect changes in pulsatile patterns and future studies should evaluate acute versus chronic hypoxia/hypercapnia. Our study used a unique model of dry apnea diving in voluntary trained apnea divers and a prerequisite for participation was an experience of 270 s as minimum apnea time. Therefore, results cannot be generalized to untrained adults.

5. Conclusions

In conclusion, even a single apnea event under dry conditions resulted in two different patterns of hormone response to apnea, with increased adrenal and reduced sex steroid levels, while pituitary hormones LH and FSH showed no clear kinetic reaction after apneic hypoxia/hypercapnia in trained apnea divers. Our results are in line with rodent hypoxia models and findings in patients suffering from intermittent hypoxia and hypercapnia. Our study strengthens hypoxia research in a human model. We recommend that future studies should focus on raising awareness of the need for careful medical exams before and during apnea diving, including monitoring of steroid and gonadotropin hormone concentrations.

Important note

The apnea experiments were performed under strict supervision and according to the highest safety standards, with continuous monitoring by an anesthetist / emergency doctor. The authors strongly advise not to replicate these experiments independently.

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Data availability

Data will be made available on request.

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