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The deconditioned and the trained heart: responses to physical exercise in pathological and physiological extreme conditions

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List of (main) Abbreviations

ANS Autonomic Nervous System

CVDs Cardiovascular Diseases

DMD Duchenne Muscular Dystrophy

ECG Electrocardiogram

HF High Frequency power

HR Heart Rate

HRV Heart Rate Variability

MD Muscular Dystrophy

NN normal-to-normal beats intervals (ms)

pNN50 percent of successive NN with differences >50 ms

POMS Profile of Mood States Scale

RMSSD Root Mean Square of Successive Differences

SCI Spinal Cord Injury

SDANN Standard Deviation of the Average NN intervals for each 5min segment of a 24h HRV recording

SDNN Mean of the Standard Deviations of all the NN intervals for each 5min segments of a 24h HRV recording

TI Therapeutic Index

TW Therapeutic window

VLF Very Low Frequency power

1. Introduction

1.1 Exercise as a medicine: CVD risk, sedentary lifestyle and the "therapeutic window"

In spite of all the efforts to prevent them, cardiovascular diseases (CVDs) remain one of the leading causes of morbidity and mortality worldwide. Currently, in Germany ischemic heart disease and stroke account for the majority of deaths each year (OECD/European Observatory on Health Systems and Policies, 2019). Beyond all the most known risk factors for CVDs (high cholesterol levels, smoking, sex, age, etc.), in these last years a sedentary lifestyle is becoming a central topic of public health in Western Countries, as a large body of literature has proven its crucial role in the determinism of cardiovascular and metabolic pathologies (Tremblay et al., 2010; Young et al., 2016; Lavie et al., 2019; Dwivedi et al., 2020; Elagizi et al., 2020; Katzmarzyk et al., 2020; Rollo et al., 2020). Furthermore, among elderly and older adults (>55 years), special populations are affected by a forced lack of physical activity, as physical and mental disabled people. For example, individuals affected by Muscular Dystrophy (MD) (Łoboda and Dulak, 2020) and spinal cord injury (SCI) persons (Farrow et al., 2020; Nash and Gater, 2020), are extremely disposed to poor physical activity, as they are (partially) excluded also from the ordinary daily activities, due to the physical limitations consequent to their specific disease.

Already almost 40 years ago, Hoffman introduced the concept of *debilitative cycle*, which refers to the forced sedentary condition of SCI individuals (Hoffman, 1986) (Figure 1).The debilitative cycle describes a condition for SCI persons where, not only the lack of regular physical exercise, but also the dramatic reduction of ordinary tasks during daily life, result in a vicious cycle that provoke worsening of functional capacity, due to the progressive impairment of cardiorespiratory and muscular systems. This results in an increased risk for cardiovascular and metabolic diseases, but also in social isolation, anxiety and depression, further decreasing the propensity to physical activity. From a poor daily activity, numerous detrimental effects on almost every organ system emerge, which in turn worsen functional capacity, leading to a further reduction of the daily physical work. The concept of *debilitative cycle* refers to all those who are not only unable to perform regular physical activity and/or participate in structured training sessions, sports or leisure activities, but also who cannot perform common daily activities (like for example house-keeping tasks, walking for shopping, climbing stairs, etc.), due to specific physical and/or psychological condition.

The good news is that this *debilitative cycle* can be reversed by practicing regular physical activity. From this perspective, exercise is considered a "medicine", exactly as a drug therapy, which can be administered for sedentarism and many other different conditions, including obesity and CVD (Pedersen and Saltin, 2015). However, with respect to traditional therapies, exercise as a medicine has the great advantage of: i) affecting simultaneously almost all organ systems, including the psychological and social sphere, and ii) being extremely cheaper for the health care systems, in comparison with traditional therapies. Therefore, regular moderate exercise has been recently proposed *"as a platform for pharmacotherapy development in cardiac diseases"* (Bei et al., 2015).

However, similarly to any drugs therapy, exercise has his own specific „therapeutic window" (TW), which must be defined on individual basis. The TW is defined in the Webster Medical Dictionary as follows: "*the range of dosage of a drug or of its concentration in a bodily system that provides safe effective therapy"* (Webster Medical Dictionary(Merriam-Webster Medical Dictionary, 2011). In other words, according to the medical dictionary, TW represents "*for drugs the well-defined range of a drug's serum concentration at which a desired effect occurs, below which there is little effect, above which toxicity occurs; the TW differs among patients and may be determined empirically*" (McGraw-Hill Concise Dictionary of Modern Medicine, 2002). The TW is known in pharmacology also as Therapeutic Index (McCallum et al., 2014).

Exercise as a medicine showed a highly specific dose-dependent efficacy in several diseases (Pedersen and Saltin, 2015; Wilkinson et al., 2016; Yang et al., 2017; Patel et al., 2019) and among disabled people, as for example SCI persons (Astorino et al., 2020; Farrow et al., 2020; Nash and Gater, 2020; Todd et al., 2020). In the same way, a large body of literature has described how physical exercise in healthy individuals can exert positive effects on the cardiorespiratory and the musculoskeletal systems (Rivera-Brown and Frontera, 2012; Hellsten and Nyberg, 2015; Hughes et al., 2018; Kramer, 2020). These effects are specifically driven not only by biomechanical characteristics of the practiced activity, but also by the training specific features, as duration, frequency and intensity: endurance/resistance training, long/short duration, intermittent/continuous training, high/moderate/low-intensity workload; all these features, taken together, will impact on circulatory and other organ systems very differently.

While regular moderate-intensity physical exercise induces cardiovascular and autonomic positive adaptations, that can increase life expectancy and improve quality of life (Myers, 2003; Hillman et al., 2008; Kramer, 2020), recently it has been suggested that as the amount and the intensity of regular exercise increase, as it may result in adverse effects on the cardiorespiratory system and other systems (O'Keefe et al., 2020). Therefore, the assumption *"the more (exercise), the better (health)"* appears misleading. On the contrary, the appropriate amount and intensity of exercise cannot be defined *a priori* but should be assessed on an *individual* basis. The latter stands for the need to select the appropriate exercise TW in healthy people, as well as in disease and disability.

From this perspective, health outcomes data from retired professional and elite athletes seem to support possible adverse effects following high training loads associated to their professional activity. The adaptations induced by training and repetitive heavy performances over years may result in detrimental health effects, as reported recently by Eijsvogels et al. (Eijsvogels et al., 2016, 2018). These authors highlighted how older athletes report more frequent negative outcomes in comparison with age matched healthy non-athletes (as for example artery calcification, atrial fibrillation and myocardial fibrosis), and other authors suggested for aged athletes an increased risk of arrythmia, atherosclerosis and sudden cardiac death. As the requested performance level pushes the athlete to perform at the "*upper limit*" of his/her physiological capacity, and continuously over the time, this "*exercise at the* *extremes*" may induce a heavy chronic hemodynamic stress on the heart (Sharalaya and Phelan, 2019). On the other hand this data are yet not conclusive and there is still debate on the health outcomes after top level professional activity, with aging, especially in relation to the specific characteristics of the different sports played (Parry-Williams and Sharma, 2020).

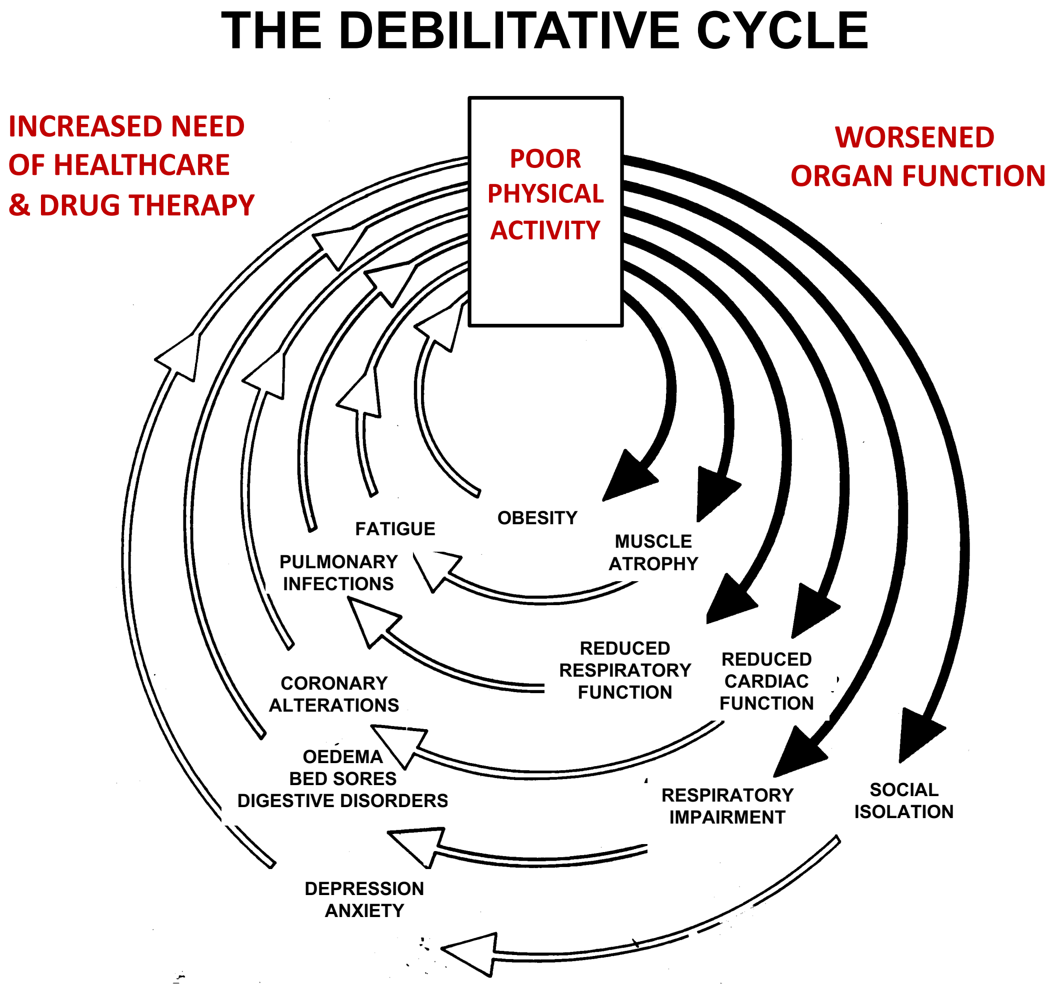

Figure 1. The debilitative cycle, an overview.

1.2 Cardiac autonomic modulation, stress and exercise: the role of HRV

Heart rate (HR) is the number of heartbeats (ventricular strokes) per minute, whereas heart rate variability (HRV) describes the fluctuation of HR around its mean. Behind this definition a long story of discoveries is hidden. The first study of arterial pulse has been conducted more than 2000 years ago, by Herophilos (ca.335–280 BC), who was the first to measure the heartbeat using a water clock to time the pulse; then the Greek physician Galen (129-201 AC) was the first to include the pulse observation in the clinical practice for diagnosis/prognosis of different diseases. Although the importance and the meaning of the pulse for human health has been defined long time ago, it is only almost 200 years that the topic of HRV is studied (Billman, 2011). This is due also to specific technological achievements, like for example the development of the electrocardiography (ECG), as we know it, by Einthoven between the 19th and the 20th century (Yang et al., 2015). On the other hand, however, the standards, physiological meaning and clinical use of HRV have been defined for the first time around 25 years ago (Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology, 1996). Therefore, looking at the published literature about HRV in the last 50 years, it may seem that the observation of a continuous variability of humans' HR is quite recent. However, the Chinese physician Wang Shu-he (265–317 A.D.), already 1700 years ago, wrote in his book, "The Pulse Classic": "*If the pattern of the heart beat becomes as regular as the tapping of a woodpecker or the dripping of rain from the roof, the patient will be dead in four day*s" (Yang Zhou-Zhong, 2007). This is probably the first observation of the HRV, by defining its decrement as a predictor of sudden cardiac death. Indeed, a huge body of literature has been published in the last decades proving the role of HRV as an independent predictor for CVD and sudden cardiac death (La Rovere et al., 2003; Sandercock and Brodie, 2006; Thayer et al., 2010; Huikuri and Stein, 2013; Sessa et al., 2018). HRV may be also useful in the emergency medicine for triage or as a prognostic tool (King et al., 2009; Mazzeo et al., 2011; Ryan et al., 2011), for survival prediction after trauma (Norris et al., 2005), risk stratification (Huikuri and Stein, 2013) and perioperative adverse cardiac event (Laitio et al., 2007; Anderson, 2017). HRV has been implemented in several fields of research and clinic areas, and can provide insights on effects of exercise on the heart in several other conditions, from health to disease (Kingsley and Figueroa, 2016; Besnier et al., 2017b; Iellamo et al., 2018; Raffin et al., 2019; Figueiredo et al., 2020). First of all, HRV represents an informative tool for all diseases where autonomic derangements typically develop, such as arterial hypertension, diabetes (Villafaina et al., 2017; Maciorowska et al., 2020; Yılmaz et al., 2020) and heart failure (Hsu et al., 2015; Tsai et al., 2020). These data clarify the role of HRV in clinical practice and its use to examine the autonomic nervous system in several pathologies, which are also related to sedentary lifestyle and forced inactivity. Recently, several papers have been published about the standards and the physiological meaning of HRV indices (Shaffer and Ginsberg, 2017; Singh et al., 2018b, 2018a).

According to these papers and to the Task Force standards (Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology, 1996), HRV is assessed in three different domains: 1) time domain, which expresses the amount of variability in the recorded data; 2) frequency domain, which decomposes the signal into single sinusoids and describes the underlying rhythms, their power and their physiological meaning; 3) non-linear domain, the most recent, which analyses the complexity and the self-similarity of the signal.

A key feature is the duration of recording, as for example selected indices in time or frequency domain should be used according to the specific duration, ranging from short-term (from 5 to 30 min) to long-term recording (from 8 to 24 hours). For example, in short-term HRV assessment, the RMSSD (i.e., the Root Mean Square of Successive Differences of NN- normal-to-normal beats intervals in ms), and the pNN50 (i.e., percent of successive NN with differences >50 ms) are used to evaluate the vagal activity, whereas for long-term recording should be used SDNN (i.e., Standard Deviation of N-N intervals in ms), which express the total variability, and the SDANN (i.e., Standard Deviation of the averages of NN intervals in all 5-min long segments), which reflects long term oscillations, as for example related to thermoregulation and neuroendocrine activity. Time domain analysis is strictly dependent from the recording duration, which must be exactly the same when comparing different measurements. In the frequency domain, for short-term assessment the index HF (i.e., High Frequency power, 0.15 to 0.4 Hz) expresses the vagal influences on HR and includes respiratory sinus arrhythmia, while in long-term recording the VLF (i.e., Very Low Frequency power, from 0.0033 to 0.04 Hz), which reflects activity in long oscillations, for example activity of renin-angiotensin system, is more appropriate. Despite the literature published, there is still a need to further develop and elucidate HRV indices, especially in the non-linear domain, and to obtain a general consensus on the meaning and use of some indices (Sassi et al., 2015). On the other hand, however, only recently the technological development allows digital recording of ECG with the high precision (i.e., 1 ms) required to assess HRV, but easy-to-use software for HRV data processing and analysis are still yet missing. Probably these are the reasons why it appears that HRV is still only a tool in research and is not getting an official place in the clinical routine or in the medical curriculum. Nonetheless, for the future, to implement digital medicine and digital health, HRV is very promising, especially for patients' remote monitoring.

On the other hand, a large quantity of studies has been conducted on the use of HRV in research, in several different areas: i) exercise/training/performance, ii) stress/resilience/adaptation; iii) crosslink between psychological traits and physiological functions. Due to the fast technological development, which lead to the next-generation of miniaturized, wearable devices, able to monitor ECG during almost every daily-life activity (including training & performance), with a very high resolution and data quality/reliability, HRV has gained an increasing attention, because the specific non-invasive methodology, which is very convenient for in-field studies (Gamelin et al., 2006; Buchheit, 2014a; Giles et al., 2016; Dobbs et al., 2019; Gilgen-Ammann et al., 2019). Indeed, HRV can describe cardiac response to different type of exercise and training (Mourot et al., 2004; Kingsley and Figueroa, 2016; Bhati et al., 2019; Gronwald and Hoos, 2020).

Moreover, HRV has been proposed as a monitoring/predicting tool for athletic performance (Plews et al., 2013) and supports studies on sex-related differences (Koenig and Thayer, 2016; Thayer et al., 2016). The interplay between cardiovascular acute and chronic response to exercise and the role of the autonomic nervous system (ANS) in finely regulating such adaptations is extremely complex and involves central and peripheral mechanisms (Fisher et al., 2015).

For this reason, HRV is becoming a valuable tool to assess stress and resilience in humans, to describe (social/occupational) stress effects on the heart and can provides important insights for psychological disease, such as depression and anxiety (Grippo et al., 2012; Sgoifo et al., 2014, 2015; Carnevali et al., 2018; Järvelin-Pasanen et al., 2018; Kim et al., 2018; Schiweck et al., 2019).

1.3 The trained and the disabled heart: adaptation to extreme conditions

Exercise and training induce over the time changes on the heart and cardiovascular system. These changes are well documented in the literature (Wilmore et al., 1995; Farrell et al., 2011; McArdle et al., 2015), and are basically related to an improved function and working efficiency of the cardiovascular system. Effects of prolonged training on the heart are summarized by lower HR at rest (bradycardia), lower HR per each sub-maximal working load (increased working efficiency), higher stroke volume, morphological changes of the myocardium, like increased wall thickness and diastolic volume of left ventricle (McArdle et al., 2015), even though the clinical interpretation of such changes still to be fully elucidated (George et al., 2012). All these changes are associated to an increased vagal tone at rest, as for example reported even after only 12-week of training (Carter et al., 2003).

Some of these changes, specifically deriving from constant long duration and high intensity training for several years, may appear as pathological, as they mimic the typical heart structural changes occurring in some disease as hypertrophic or dilated cardiomyopathy, especially considering the “normal” operating ranges of the human heart. Therefore, already in the 19th Century the concept of “athlete’s heart” was introduced, referring to the bradycardia and cardiac enlargement typical of athletes (Oakley, 2001). The *cardiac remodeling* occurring in athletes is specifically functional to the performance and can demonstrate the effect of training on the heart, which slowly occurs according to the training load and duration at any stage, increasing step by step, being the *athlete’s heart* the extreme condition, let’s say the *zenith* of the heart’s physiological capacity.

Furthermore, it has been proven that such adaptations are driven by performance and training features, distinguishing between *static* and *dynamic* components of each specific sports, thus between resistance and endurance athletes, as reported by Prior et al. (Fagard, 2003; Prior and La Gerche, 2012) and confirmed by a later meta- analysis (Pluim et al., 2000).

Recently, this assumption has been challenged, by showing how the differences between the heart adaptation after long-term endurance training and long-term resistance training are smaller, being essentially related to the left ventricular end-diastolic diameter and volume only, which were significantly higher in endurance athletes, as reported by Utomi et al. (Utomi et al., 2013).

If we consider the athlete’s heart as the *zenith*, the highest performance level reachable, on the opposite side, to the *nadir*, is located the disabled heart. In this work, the term *disabled heart* refers to the heart damaged by a specific disease which affects the heart itself, whereas the term *impaired heart*, refers to the heart not itself damaged, but which suffers for consequences following forced inactivity or other non-cardiac diseases. Is exercise training always positive for such *disabled* or *impaired heart*? Would exercise improve functional capacity and overall health and wellbeing, as for healthy individuals, according to duration, intensity and frequency, or would instead represent a high risk? Would be exercise dangerous in specific clinical conditions (GATES et al., 2002)?

Exercise for a disabled heart might represent an *extreme* condition, as it can turn out in adverse outcomes, when the heart is not able to match the demands of a physical performance. Indeed, exercise may be described as extreme condition *per se*, for example considering a top-level athlete performing at the border of the physiological known limit or in an extreme environment, but also considering disabled people, as a paraplegic running a wheelchair marathon in the Paralympic games.

The definition of the adjective *extreme* can refer to several aspects: indicating outermost or farthest; attaining to the greatest or highest degree of something: indicating a very dangerous or difficult thing. However, considering all these meaning nuances, physical performance at the top level, together with physical performance of disabled people, could be considered as *extreme*.

Therefore, the question is whether exercise might be always positive, and to which extent are humans, specifically referring to the heart, able to physical perform and adapt to extreme conditions, as hostile environments, severe physical disability, psychological high-stressful situations, forced inactivity (almost motionless) like in bed rest.

The aim of this work is to explore the adaptation capacity of the heart and cardiovascular system to these extreme conditions, which are reported in the following papers. A secondary aim is to explore the use of HRV as a marker of heart response to emotion and cognition, as the ANS, and specifically the vagus nerve is finely regulating heart function and integrates also cognitive and phycological traits. In this sense, HRV might become a good candidate to bridge the gap between physiology and psychology, as postulated by the neuro-visceral integration theory (Thayer and Lane, 2009; Thayer et al., 2009; Shaffer et al., 2014; Smith et al., 2017; Wulsin et al., 2018).

2. Own publications

The focus of the presented publications is the description of cardiac response to exercise under special conditions, in particular as for morphological and autonomic adaptations. In details, the effect of long-term endurance training (chronic) and the effect of 60-day resistance training (acute) have been investigated in condition of forced sedentary lifestyle (i.e., among SCI endurance athletes and healthy individuals during long-term bed rest, respectively), whereas the heart acute adaptation to a single-match performance have been evaluated in men affected by MD (Muscular Dystrophy).

Moreover, cardiac autonomic modulation, assessed by HRV analysis, has been studied as a tool to monitor/predict performance under extreme environmental conditions, among professionals, i.e., i) competitors of a subarctic Ultramarathon (690 km), and ii) firefighters performing repetitive bouts of resistive exercise during a fire extinguish task in a container set on fire. HRV has been also tested in mirroring participants' psychological traits, as for example resilience, risk taking behavior, profile of mood state (POMS), during different performances and in various extreme environments, to investigate the possibility of HRV as a connection between physiology and psychology.

The following aims have been proposed:

1. <u>The disabled heart</u>: To analyze the ability of the heart to match the demands of a physical performance even under the limited physiological abilities of a disabled heart, as in the case of MD individuals. Indeed, given that muscular dystrophy affects not only the skeletal muscles but also the myocardial tissue (since the early pathology stages), the capability of this disabled heart to match the increasing metabolic/energetic demands are not given as foregone.
2. <u>The impaired heart</u>: To assess in SCI individuals the effects of long-tern endurance training (i.e., over 5 years), in comparison to able-bodied individuals, as for morphological adaptation and heart function changes.
3. <u>The sedentary heart</u>: To evaluate the time course of cardiovascular and cardiac autonomic modulation changes induced by a short-term, high-intensity training protocol to counteract cardiac deconditioning and orthostatic instability, after long-term cardiac unloading based on the model of long-term -6 degrees bed rest (60 days), which represents a pathological condition of extreme sedentary lifestyle (and sedentary heart).
4. <u>The trained heart</u>: To determine whether the cardiac autonomic modulation among professionals (endurance athletes and firefighters) could monitor/predict physical performance in extreme conditions (i.e., in extreme cold and in extreme hot environments respectively), and to explore the use of HRV to connect physiology and psychology, as a marker of stress, resilience and risk-taking behavior among fire department officers, and as a marker of psychological correlates for ultramarathon runners in extreme cold/hostile environment.

2.1 First paper. The *disabled heart*: the physical performance

Maggioni MA, Rampichini S, Cè E, Agnello L, Veicsteinas A, Merati G. (2008) *Cardiac and autonomic adaptations to a wheelchair hockey match in athletes with muscular dystrophy.* Sport Sci. Health 4, 59–63.

In this paper the acute effects of a physical performance, analyzed before, during and after a single match, on the disabled heart are investigated. Muscular Dystrophies (MD) are a class of genetic, life-threatening, progressive, neuromuscular diseases, whom severity may largely vary according to the specific type, being the Duchenne (DMD) the most serious (Wang et al., 2010; Gilbreath et al., 2014; Schorling et al., 2017; Butterfield, 2019). MD determines a progressive wasting and weakening of muscle tissues, including the myocardium. Symptoms range from movement impairments, to severe limitation of respiratory and cardiac function, with negative cardiac outcomes (Hermans et al., 2010; Meyers and Townsend, 2019; Łoboda and Dulak, 2020). The quality of life in these patients is crucial, as no effective therapy is available; therefore, exercise may play an important role not only to conserve a residual motor ability, but also fostering social life and psychological well-being (Ng et al., 2018). However, the ability of the heart to adapt and match the demands of a physical performance needs to be evaluated, with the aim of shaping adequate training programs and preventing adverse outcomes.

In this study, we enrolled 30 men affected by different types of MD, clustered according to the MD severity level into two groups: Duchenne MD (DMD, n= 13) and others milder MD, (OMD, n = 17). This was one of the first in-field study monitoring HR and HRV in the setting of a real electric-wheelchair hockey match, during the regular season. Electric-wheelchair hockey is a specific discipline developed to allow all participants to compete at the same level, independently from their residual ability. A detailed description of electric-wheelchair hockey is available at the following link https://www.sports.org.au/electric-wheelchair-hockey (Disability Sports Australia, 2020).

HR data were collected with a heart rate monitor, before (15 min), during (the last 20 min) and after (10 min) a single electric-wheelchair hockey match. HRV was assessed in time, frequency and non-linear domains in a subsample of DMD only (DMDs, n=9). Results showed:

1. Before the game, compared to diurnal epidemiological data of healthy matched individuals, both groups, DMD and OMD, had a significantly higher HR.
2. During the game, HR increased further, with a significant difference between groups: the HR in DMD group was lower in comparison to HR of OMD group.
3. After the game, HR decreased significantly in both groups, with no differences, although in the recovery, the HR decrease in comparison with HR during game in DMD was significantly lower than in OMD.
4. HRV, assessed in DMDs subgroup, showed a significant withdrawn of parasympathetic tone during the game, with a shift toward sympathetic predominance.

Despite the pre-game tachycardia, both DMD and OMD groups seemed able to adapt and match the demand of a physical effort during the game, by further increasing HR, even though DMD groups was able to increase HR to a significant less extent compared to OMD group, and showed during recovery a lower decrease of HR.

Maggioni MA, Rampichini S, Cè E, Agnello L, Veicsteinas A, Merati G. (2008)
Cardiac and autonomic adaptations to a wheelchair hockey match in athletes with muscular dystrophy.
Sport Sci. Health 4, 59–63
https://doi.org/10.1007/s11332-008-0068-0

2.2 Second paper. The *impaired heart:* exercise in the debilitative cycle

Maggioni MA, Ferratini M, Pezzano A, Heyman JE, Agnello L, Veicsteinas A, Merati G. (2012) *Heart adaptations to long-term aerobic training in paraplegic subjects: an echocardiographic study*. Spinal Cord 50, 538–42

Aim of this case-control study was an echocardiographic comparison between trained and untrained spinal cord injury (SCI) men, and between trained SCI individuals and healthy matched trained able-bodied men. Among SCI, according to the lesion level, the heart may suffer from defective innervation, when the lesion level is upper than the 6th thoracic vertebra. In addition, the nervous communication with the sublesional vascular districts is interrupted, therefore causing a reduced vasomotion, which in turns induces *blood pooling* in the periphery. The latter decreases venous return and heart filling volume. Over the time, the blood pooling generates myocardial atrophy and dramatically reduces heart functional capacity.

The objective of the study is therefore two-folded:

1. to assess the morphological and functional heart adaptation after long-term endurance training among SCI men, by comparing trained vs. untrained individuals.

2. to determine whether possible heart adaptations to endurance training are similar to that observed in healthy trained peers.

To this aim were enrolled: 10 SCI men aerobically trained for >5 years (SCI_T) and 7 untrained SCI men (SCI, total n=17) to be compared with 10 healthy peers aerobically trained for >5 years (ABL_T) and 8 healthy untrained peers (ABL, total n=18). Peak oxygen consumption (VO_2peak) was assessed in SCI participants only, with a cardiopulmonary exercise test on a wheelchair ergometer, up to maximal volitional exhaustion. Training records, as for volume and frequency, were collected with a questionnaire and cross referenced with the available medical screenings for participating in official competition, performed in the previous 5 years.

Results showed a VO_2peak of SCI_T persons significantly higher compared to VO_2peak of untrained SCI, confirming the functional adaptation following long-term endurance training reported for non-paraplegic individuals (Hellsten and Nyberg, 2015). Furthermore, SCI_T in comparison with untrained SCI had a higher intra-ventricular septum thickness (+18%), posterior wall thickness (+17%) and normalized heart mass (+48%), and the same was found for ABL_T, with respect to untrained peers (+4%; +2%; +5% respectively), though to a lesser extent. However, SCI_T, when compared to ABL_T, revealed a lower end-diastolic volume and left ventricular ejection fraction.

The study confirms the permanence of a compromised heart morphology and function secondary to SCI (i.e., reduced filling capacity and ejection fraction), but demonstrate how, on the other side, regular aerobic training can mitigate such adverse outcomes, significantly improving peak oxygen consumption and therefore physiological functions. Such changes seem to persist over the time, consistent with those reported for non-paraplegic individuals. Furthermore, these morphological and functional adaptation, can reduce cardiovascular risk.

Maggioni MA, Ferratini M, Pezzano A, Heyman JE, Agnello L, Veicsteinas A, Merati G. (2012)
Heart adaptations to long-term aerobic training in paraplegic subjects: an echocardiographic study.
Spinal Cord 50, 538–42
https://doi.org/10.1038/sc.2011.189

2.3 Third paper. The *astronaut's heart*: exercise-based countermeasures

Maggioni MA*, Castiglioni P*, Merati G, Brauns K, Gunga H-C, Mendt S, Opatz O, Rundfeldt LC, Steinach M, Werner A, Stahn AC. (2018) *High-intensity exercise mitigates cardiovascular deconditioning during long-duration bed rest*. *These Authors contributed equally, Front. Physiol. 9, 1553

The focus of this paper is to evaluate possible countermeasures to cardiovascular deconditioning, in terms of orthostatic intolerance and resting tachycardia. Indeed, cardiovascular deconditioning is known as one of the most frequent adverse outcomes of microgravity exposure, or long-term unloading of the cardiovascular system, due for example to post-trauma or post-surgery forced bed lying. Head-down-tilt bed rest (HDT), with the head at -6 degrees with respect to the horizontal line, mimics the changes in hemodynamics and autonomic cardiovascular control induced by microgravity and it is well known as an Earth analog for space missions (Besnier et al., 2017a). As part of an European Space Agency sponsored long-term bed rest study, it was evaluated how high-intensity, short-duration, low-limbs resistance exercise can influence the time course of cardiovascular hemodynamics and cardiac autonomic modulations during HDT.

Measurements sessions were performed by comparing all the supine positions at HDT-6 degrees (i.e., HDT day 2, day 28 and day 56), and also in day 7 before HDT (BDC-7) and in day R+10 (R: recovery after HDT) both in the horizontal lying position (i.e., 0 degrees). Moreover, before and after HDT, the reactivity of the cardiovascular and autonomic response was analyzed by collecting data in both supine and sitting position.

Twenty-three healthy young men were randomly allocated to two groups: training (TRAIN, $n = 12$) and non-training (CTRL, $n = 11$) before the 60-day HDT. The TRAIN group underwent a resistance training program with reactive jumps on a sledge-system (5-6 times/week, 20 min/session, 80% of body weight) (Kramer et al., 2010, 2017b), to maintain continuously the lying position and reproducing the conditions of microgravity, where only hydraulic resistance may be used to generate workload, whereas the CTRL group did not train. Continuous finger blood pressure, impedance and electrocardiography data were collected for 10 min in all sessions and positions.

During long-term HDT, HR increased ($p < 0.02$) and parasympathetic tone decreased in the CTRL group ($p < 0.0001$) only, while the TRAIN group showed only a slight trend. After 60-day HDT, signs of orthostatic instability were still present in the CTRL group: by comparing values collected in supine to those collected in sitting, it appeared that CTRL individuals could not dynamically adapt to the posture change, showing higher supine HR and a sympathovagal balance shifted towards parasympathetic predominance in sitting vs supine position, whereas TRAIN seemed to be less affected and to have almost recovered. Therefore, even a low-body, high-intensity, short-duration exercise could effectively mitigate cardiovascular deconditioning in the TRAIN group. In addition, as for CTRL group the 10-day recovery appeared to be not sufficient to completely compensate the cardiovascular deconditioning due to 60-day HDT.

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High-Intensity Exercise Mitigates Cardiovascular Deconditioning During Long-Duration Bed Rest

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Head-down-tilt bed rest (HDT) mimics the changes in hemodynamics and autonomic cardiovascular control induced by weightlessness. However, the time course and reciprocal interplay of these adaptations, and the effective exercise protocol as a countermeasure need further clarification. The overarching aim of this work (as part of a European Space Agency sponsored long-term bed rest study) was therefore to evaluate the time course of cardiovascular hemodynamics and autonomic control during prolonged HDT and to assess whether high-intensity, short-duration exercise could mitigate these effects. A total of $n = 23$ healthy, young, male participants were randomly allocated to two groups: training (TRAIN, $n = 12$) and non-training (CTRL, $n = 11$) before undergoing a 60-day HDT. The TRAIN group underwent a resistance training protocol using reactive jumps (5–6 times per week), whereas the CTRL group did not perform countermeasures. Finger blood pressure (BP), heart rate (HR), and stroke volume were collected beat-by-beat for 10 min in both sitting and supine positions 7 days before HDT (BDC−7) and 10 days after HDT (R+10), as well as on the 2nd (HDT2), 28th (HDT28), and 56th (HDT56) day of HDT. We investigated (1) the isolated effects of long-term HDT by comparing all the supine positions (including BDC−7 and R+10 at 0 degrees), and (2) the reactivity of the autonomic response before and after long-term HDT using a specific postural stimulus (i.e., supine vs. sitting). Two-factorial linear mixed models were used to assess the time course of HDT and the effect of the countermeasure. Starting from HDT28 onwards, HR increased ($p < 0.02$) and parasympathetic tone decreased exclusively in the CTRL group ($p < 0.0001$). Moreover, after 60-day HDT, CTRL participants showed significant impairments in increasing cardiac sympathovagal balance and controlling BP levels during postural shift (supine to sitting), whereas TRAIN participants did not. Results show that a 10-day recovery did not compensate for the cardiovascular and autonomic deconditioning following

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60-day HDT. This has to be considered when designing rehabilitation programs—not only for astronauts but also in general public healthcare. High-intensity, short-duration exercise training effectively minimized these impairments and should therefore deserve consideration as a cardiovascular deconditioning countermeasure for spaceflight.

Keywords: heart rate variability, hemodynamics, countermeasure, cardiovascular deconditioning, posture, long-term bed rest

INTRODUCTION

Upcoming deep space missions such as Martian expeditions will require exposure to up to 1,000 days in microgravity (Horneck, 2006). Space agencies are thus investigating adverse health effects of long-term missions and their possible countermeasures in order to reduce detrimental consequences for astronaut health (Aubert et al., 2016; Bergouignan et al., 2016; Frippiat et al., 2016; White et al., 2016; Lang et al., 2017). Space analogs simulating prolonged gravity changes therefore play a crucial role (Ploutz-Snyder, 2016). Bed rest with −6 degrees head-down tilt (HDT) is one of the best conditions to mimic the effect of long-term weightlessness on the human body—even within the limitations of this model. HDT shifts fluids from the lower domain to the upper region of the body, similar to the fluid centralization observed in spaceflight (Pavy-Le Traon et al., 2007; Hargens and Vico, 2016; Watenpaugh, 2016). Bed rest models also allow for the investigation of some of the effects of immobilization, secondary to hospitalization, and physical inactivity. Indeed, elderly patients spend over 80% of their hospital admission confined to their bed (Vernikos and Schneider, 2010; Baczynska et al., 2016), and physical inactivity is one of the leading causes of death in Western countries (Blair, 2009). Therefore, investigating the physiological consequences of physical inactivity and designing effective countermeasures is essential for planning future long-term space missions as well as for public health and rehabilitation purposes. Weightlessness negatively affects several physiological functions. For example, it can cause deconditioning of the cardiovascular system, which may be characterized by higher resting heart rate with altered autonomic control associated with orthostatic intolerance (Blomqvist et al., 1994; Sigaudo et al., 1998; Fortrat et al., 2001; Custaud et al., 2002). Despite research spanning at least four decades on weightlessness-associated cardiovascular alterations (Pavy-Le Traon et al., 2007; Hargens and Vico, 2016), the exact time courses of changes in hemodynamic regulation and autonomic cardiovascular control induced by long-term spaceflight are not fully understood (Liu et al., 2015; Aubert et al., 2016). Moreover, several countermeasures for cardiovascular deconditioning have already been tested (e.g., volume loading, lower-body negative pressure, hypergravity; Wang et al., 2011; Stenger et al., 2012; Jeong et al., 2014; Li et al., 2017), but exercise is the most investigated countermeasure (Blaber et al., 2009; Petersen et al., 2016; Ploutz-Snyder, 2016). However, despite the consensus on physical activity as a countermeasure, the type and intensity of the exercise are undergoing further investigation. Common exercise countermeasures include aerobic (Pagani et al., 2009; Cavanagh et al., 2017; Demontis et al., 2017) and resistive exercise (Holt et al., 2016; Demontis et al., 2017), as well as in combination with whole-body vibration (Belavý et al., 2010). Recent findings show high-intensity interval training (HIIT) to be salutary in cardiovascularly compromised persons (Ramos et al., 2015; Fleg, 2016; Hussain et al., 2016), improving aerobic capacity, endothelial, and left-ventricular function, vasomotor function, and blood pressure (Hussain et al., 2016). So far, however, HIIT has rarely been implemented to counteract cardiovascular deconditioning and orthostatic intolerance in microgravity settings (Hughson et al., 1994; Greenleaf, 1997; Hastings et al., 2012; Hargens et al., 2013). This study therefore aimed to evaluate whether short-duration HIIT is an effective countermeasure against cardiovascular deconditioning and orthostatic intolerance induced by 60 days of head-down-tilt bed rest. To achieve this aim, we compared subjects doing HIIT with a control group and investigated 1) the time course of hemodynamic changes and adaptations of the cardiovascular autonomic control during 60-day HDT, and 2) the cardiovascular response to a postural test performed before and after the bed rest confinement. As for the HIIT exercise, we administered specific lower body resistance training that provides neuromuscular force solicitation: the reactive jump protocol in a sledge jump system (Kramer et al., 2010, 2017b).

METHODS

This research was performed as part of the European Space Agency (ESA) sponsored study "Reactive jumps in a Sledge jump system as countermeasure during Long-term bed rest—RSL Study" at the DLR *:envihab* (German Aerospace Agency (DLR), Cologne, Germany), between 2015 and 2016. Details related to the core project design, recruitment, randomization of volunteers, and training protocol are reported elsewhere (Kramer et al., 2017a,b). The study was conducted in accordance with the Declaration of Helsinki for Medical Research Involving Human Subjects (revision October 2013) and was approved by the ethics committee of the Northern Rhine Medical Association in Düsseldorf, Germany (see Kramer et al., 2017a). After the purpose, procedures, and known risks of the tests had been explained to the participants, each participant gave written informed consent. In brief, the study consisted of 15 days of baseline data collection (BDC−15 through BDC−1), 60 days of HDT bed rest (HDT1 through HDT60), and 15 days of recovery (R+0 through R+14). During the 60 days of −6 degrees HDT, the reactive jump training was administered as a countermeasure in one randomly selected subsample (TRAIN: training), whereas the other subsample (CTRL: control) did not perform any physical training (see section subjects below). The training protocol was performed using a sledge jump system (Novotec Medical GmbH, Pforzheim, Germany) composed of a lightweight sledge sliding on rails. Cylinders pull the sledge toward the plates with force exerted on the subject by adjusting the pressure settings within the cylinders. The participant was fixed supine to the sledge with shoulder straps and with feet on force plates. Participants would then perform countermovement jumps while receiving feedback on jump height and peak force from a monitor. Participants in the TRAIN group underwent the training protocol starting from HDT1. Each training session consisted of repetitive jumps and different series of countermovement jumps with an average load equal to or above 80% of the participant's body weight. Sessions lasted about 20 min, including preparation. Training took place in the afternoon between 2 and 6 pm, 5–6 times per week, for a total of 48 sessions during the 60-day bed rest. A comprehensive description of the sledge system, the training method, and timeline is reported elsewhere (Kramer et al., 2017a,b).

Subjects

Data were collected from 23 young, healthy, male participants (baseline: age 29 ± 6 [m ± SD] years, weight 77 ± 7 kg, height 181 ± 6 cm), who were not involved in competitive or professional sport activities at the time of the study (see Kramer et al., 2017a,b for details on inclusion and exclusion criteria). Participants were randomly allocated to a training group (TRAIN, $n = 12$, age 30 ± 7 years, weight 78 ± 7 kg, height 181 ± 7 cm) or to a control group (CTRL, $n = 11$, age 28 ± 6 years, weight 76 ± 8 kg, height 181 ± 5 cm), and were matched based on anthropometry (Kramer et al., 2017a). One subject of the TRAIN group and one of the CTRL group were re-ambulated after 49 and 50 days of HDT (instead of 60 days), respectively, for medical reasons (Kramer et al., 2017a). Notably, this did not affect their completion of the recovery phase and all the scheduled measurements were collected. Accordingly, these subjects were included in the data analysis.

Data Collection

To evaluate short-, mid-, and long-term exposure to HDT, autonomic cardiovascular and hemodynamic data were collected on the 2nd (HDT2), on the 28th (HDT28), and on the 56th (HDT56) day of HDT. To evaluate the response to a postural stimulus, we also collected the identical data 7 days before the start of HDT (BDC−7) and 10 days after the end of HDT (R+10, R+0 being the first day of recovery) in both sitting and supine positions (**Figure 1**). In each session, a time series of physiological data were recorded for 10 min. During the lay-to-sit challenge (in BDC−7 and R+10) data were first recorded for 10 min in the supine position and then for an additional 10 min immediately after the change of posture to the sitting position. Recordings included blood pressure at the finger artery (BP) measured via continuous finger plethysmography and one-lead electrocardiogram (ECG). Both were sampled at 200 Hz. Beat-by-beat stroke volume (SV), cardiac output (CO), and total peripheral resistance (TPR) were obtained using impedance cardiography (TensoScreen®, Medis Germany). All measurement sessions were conducted between 9 and 12 am (before lunch), at least 18 h after the previous training session. Participants were required to avoid caffeine consumption during the 4 h leading up to the measurements, and were instructed not to move, talk, or fall asleep during the recordings.

Data Analysis

An expert operator visually inspected the ECG and BP signals, identifying and manually removing possible artifacts and premature beats. Beat-by-beat time series of normal-to-normal R-R intervals were derived from the ECG tracing for heart rate variability (HRV) analysis. Beat-by-beat values of systolic BP (SBP) and diastolic BP (DBP) were obtained from the BP signal. Beat-to-beat series of R-R intervals and DBP values were interpolated linearly at 10 Hz and resampled at 5 Hz. The Welch periodogram was estimated by splitting the resampled series in 90% overlapping Hann windows of 240 s in duration, computing the FFT spectrum in each window, and by averaging the spectra over all the windows. The final periodogram was smoothed with a broadband procedure that averages adjacent spectral lines with a moving average filter whose order increases with the frequency from 3 to 11 (Di Rienzo et al., 1996). Following the guidelines on HRV analysis (Task Force of the European Society of Cardiology the North American Society of Pacing

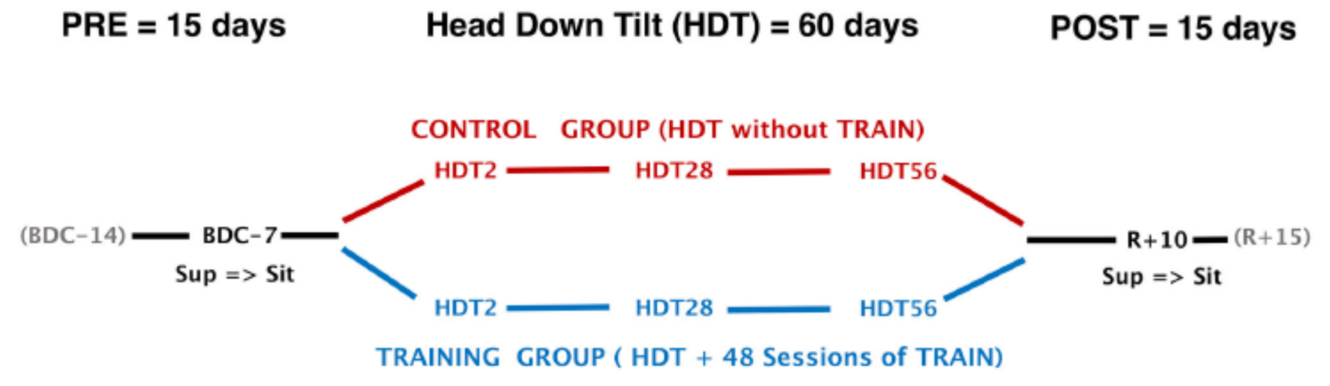

FIGURE 1 | Study design and timeline of data collection. HDT, head-down tilt; TRAIN, reactive jumps training; BDC−7, Baseline Data Collection (7 days before start of HDT); R+10, Recovery data collection (10 days after the end of HDT); Sup, measurements in supine position; Sit, measurements in sitting position.

Electrophysiology, 1996), the power spectrum of R-R intervals was integrated over a very-low-frequency (VLF, 0.005–0.04 Hz), a low-frequency (LF, 0.04–0.15 Hz), and a high-frequency band (HF, 0.15–0.40 Hz). The ratio between LF and HF powers was calculated as an index of cardiac sympathovagal balance (i.e., LF/HF). The LF power was also derived for the DBP spectrum as an index of sympathetic modulations of the vascular tone (Castiglioni et al., 2007). The short-term fractal index DFA1 was estimated by applying detrended fluctuation analysis to the beat-by-beat R-R interval series (Peng et al., 1995) and by considering block sizes not larger than 16 beats. DFA1 reflects changes in the cardiac autonomic tone, which increases when the sympathovagal balance increases or the vagal tone decreases (Tulppo et al., 2001; Castiglioni et al., 2011). The mean breathing rate was evaluated as the central frequency of the power spectrum of ECG-derived respiration (EDR) signal. The EDR signal reflects the respiratory movements of the thorax as modulations of the amplitude of the QRS complex (Schmidt et al., 2017).

Statistics

Descriptive statistics have been reported as means and standard deviations (m ± SD) unless stated otherwise. To evaluate

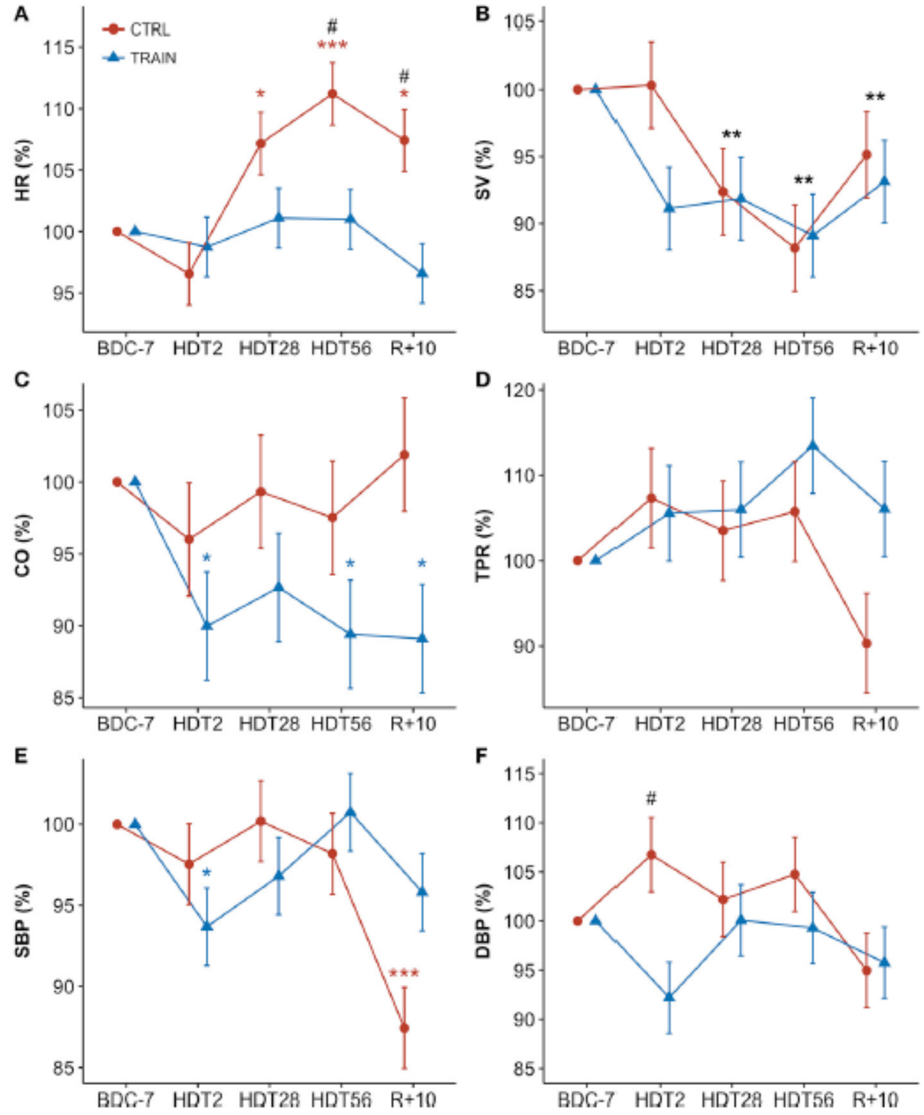

FIGURE 2 | (A–F) Time courses of hemodynamic variables for CTRL (red circles) and TRAIN (blue triangles) groups. Measurements time points in supine position: 7 days before (BDC−7) and 10 days after (R+10) HDT, and on the 2nd (HDT2), 28th (HDT28) and 56th (HDT56) day of HDT. Data are presented as marginal means ± SE of percent changes from baseline values (with BDC−7 supine =100%) at each time point. Colored asterisks indicate significance compared to BDC−7 within the single group. Black asterisks show significant difference from baseline in the whole sample of participants (when only the factor Time - and not the factor Group or their interaction - is significant). The pound sign denotes significant differences between groups at each time point. **(A)** HR, Heart Rate; **(B)** SV, Stroke Volume; **(C)** CO, Cardiac Output; **(D)** TPR, Total Peripheral Resistance; **(E)** SBP, Systolic Blood Pressure; **(F)** DBP, Diastolic Blood Pressure. $^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$, $^{\#}p < 0.05$.

the time course of cardiovascular changes during and after bed rest compared to baseline, we expressed data of HDT2, HDT28, HDT56, and R+10 as percentage changes from BDC−7 by dividing the values recorded in each HDT time point by the corresponding value measured in BDC−7 supine (which therefore corresponds to the 100% reference). A log transformation was applied to frequency-domain indices to attain normal distribution (Castiglioni et al., 1999). Because of the properties of the logarithm, the normalized variables were expressed as the difference between the log-transformed value in each time point and the log-transformed value in the baseline, which therefore corresponds to the reference zero level. Two-factorial linear mixed models were then used to assess the time course of cardiovascular changes in supine position within and between subjects. Subjects were entered as random factors and bed rest Time (HDT2, HDT28, HDT56, and R+10) and intervention Group (CTRL and TRAIN) were included as fixed factors. Significant effects of Time and Group or their interaction were followed up using contrasts (with BDC−7 as a reference for Time). When only the factor Time was significant, contrasts were performed irrespective of the intervention (i.e., CTRL and TRAIN groups were pooled).

As for the postural test (i.e., the shift from supine to sitting) performed before and after HDT, variables were expressed as *delta scores*. The *delta score* corresponds to the difference (Δ) between the value measured before bed rest (at BDC−7) and the respective value measured after bed rest (at R+10) per group (CTRL and TRAIN) and position (supine and sitting). Therefore, *delta scores* are changes from baseline values (i.e., BDC−7) and express the effects of bed rest according to each group and each posture. Mixed models were used to assess within-participant and between-participant differences in *delta scores*. Body position and intervention group were included as fixed factors and subjects as random factors. When the factor Posture, or Group, or their interaction was significant, contrasts were performed to follow up on single comparisons and corrected for multiple comparisons by a sequentially rejective correction procedure. To test whether bed rest had a significant effect in a given group and posture, contrasts were used to determine whether each *delta score* differed significantly from zero (non-zero contrasts). Covariance matrices were determined by restricted maximum likelihood (REML) estimation. *P*-values were obtained using Satterthwaite's approximation for denominator degrees of freedom. Normality and homogeneity were checked via visual inspections of plots of residuals against fitted values. The level of significance was set at $\alpha = 0.05$ (two-sided) for all testing. All comparisons were corrected for multiple comparisons using a sequentially rejective correction procedure (Hochberg, 1988). To maximize sensitivity for detecting true differences while maintaining control over family-wise Type I errors, we followed the recommendation of choosing smaller, more focused families rather than broad ones (Westfall et al., 2011). All statistical analyses and graphical illustrations were carried out using the software package R (R Core Team, 2016) Mixed models were run using the packages lme4 and lmerTest (Bates et al., 2014; Alexandra Kuznetsova et al., 2016). Adjusted means were calculated using the lsmeans package (Lenth, 2016) and htmlTable (Max Gordon, 2017). Figures were created using ggplot2, ggpubr, and cowplot (Wickham, 2016; Alboukadel Kassambara, 2017; Claus O. Wilke, 2017).

TABLE 1 | HDT time course: significance of Time and Group factors and their interaction based on linear mixed models analysis (see text for abbreviations).

	Significance p		
	Time	**Group**	**Time × Group**
HR	<0.001	<0.05	<0.01
SV	<0.05	0.43	0.16
CO	0.67	0.055	0.65
SBP	<0.001	0.72	<0.01
DBP	0.12	0.18	0.06
TPR	0.09	0.31	0.26
RRI SPECTRAL POWERS:			
log HF	< 0.001	0.19	<0.01
log LF	< 0.001	0.74	<0.01
log VLF	< 0.001	0.75	0.20
log LF/HF	0.055	0.28	0.61
DFA1	<0.05	0.15	0.06
DBP SPECTRAL POWERS:			
log LF	0.38	0.37	0.21

RESULTS

Time Course of Hemodynamic Variables During HDT

Figure 2 shows percent changes in hemodynamic values from baseline (BDC−7 supine) measured during HDT and recovery. **Table 1** reports the results of the linear mixed models analysis. The factor Time and its interaction with Group were significant for HR. Accordingly, HR was higher than at baseline from HDT28 up to the recovery phase (R+10) in CTRL participants, while not exhibiting changes in the TRAIN group. In particular, the difference between groups in HR changes was statistically significant near the end of bed rest (HDT56) and during recovery (R+10). Time was also a significant factor for SV, which decreased during HDT, recovering only partially in R+10. The factor Group was marginally significant for CO, with values lower than baseline for only the TRAIN group. The factor Time and its interaction with Group were highly significant for SBP. **Figure 2** shows a marked fall in SBP during recovery in the CTRL group only. DBP showed a marginal significance for the interaction between Group and Time. No factors were significant for TPR (**Figure 2**) and EDR; the respiratory rate did not change significantly during and after HDT.

Time Course of Autonomic Indices During HDT

Figure 3 shows percent changes in autonomic indices from baseline. **Table 1** shows the results of the linear mixed models. Since percent changes of spectral powers were log-transformed

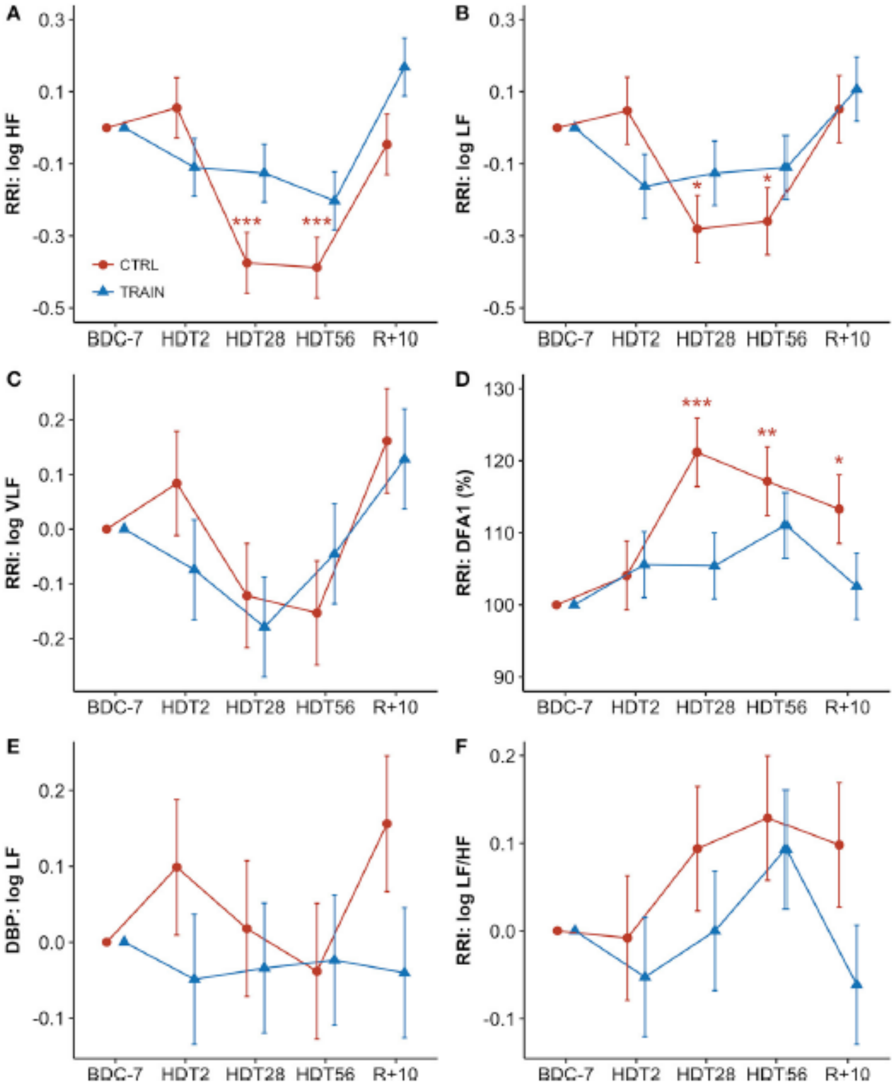

FIGURE 3 | (A–F) Time courses of autonomic variables for CTRL (red circles) and TRAIN (blue triangles) groups. Measurements time points in supine position: 7 days before (BDC−7) and 10 days after (R+10) HDT, and on the 2nd (HDT2), 28th (HDT28) and 56th (HDT56) day of HDT. Data are presented for each time point as marginal mean ± SE of differences with respect to baseline supine position (for spectral powers, BDC−7 supine = 0) or of percent changes from baseline supine position (for DFA1, BDC−7 supine = 100%). Colored asterisks indicate significance compared to BDC−7 within the single group. RRI, R-R intervals; **(A)** HF, High-Frequency power; **(B)** LF, Low-Frequency power; **(C)** VLF, Very-Low-Frequency power; **(D)** DFA1, short-term fractal index by detrended fluctuations analysis; **(E)** LF of DBP: Low-Frequency power of Diastolic Blood Pressure; **(F)**: LF/HF, Low-Frequency to High-Frequency powers ratio $^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$.

before the statistical test, they are reported as differences vs. zero, i.e., the baseline reference (see Methods). The factor Time and the interaction between Time and Group were highly significant for the HF and LF powers of RRI (**Table 1**). Both these powers had values lower than baseline at HDT28 and HDT56 for the CTRL group only. Time was a significant factor and the interaction between Time and Group was close to the 5% significance threshold. This was also the case for DFA1, whose profile mirrored the profile of the HF power, with a significant increase at HDT28 and HDT56 for the CTRL group only. In this case, however, the increase was consistently statistically significant during recovery as well. As for the LF/HF powers ratio, Time was the only factor close to statistical significance (**Table 1**). No factors were significant for the LF power of DBP.

Hemodynamic Response to the Postural Test

Table 2 reports descriptive statistics of hemodynamic data in supine and sitting positions at BDC−7 and R+10. Not only before but also after bed rest, the shift from supine to sitting posture appears associated with an increase in HR, DBP, and TPR, and with a decrease in SV and CO in both groups. However, the bed rest had a different effect on the amplitude of the changes in the two groups, as reported in **Figure 4** (i.e., *delta scores* of

TABLE 2 | Postural test: mean (SD) in the supine (Sup) and sitting (Sit) position before (BDC−7) and after (R+10) bed rest (see text for abbreviations).

		CTRL		*TRAIN*	
	Time	**Sup**	**Sit**	**Sup**	**Sit**
HR (bpm)	BDC−7	58.5 (7.4)	69.1 (8.3)	64.2 (9.1)	70.4 (7.8)
	R+10	62.7 (7.6)	70.2 (5.9)	62.1 (10.5)	68.2 (7.8)
SV (mL)	BDC−7	106.7 (18.7)	81.5 (14.0)	101.6 (14.1)	76.8 (12.5)
	R+10	101.3 (17.9)	75.6 (11.8)	94.6 (15.9)	70.9 (9.0)
CO (L/min)	BDC−7	6.1 (1.1)	5.5 (1.0)	6.5 (1.1)	5.3 (0.8)
	R+10	6.2 (1.2)	5.2 (0.8)	5.8 (1.3)	4.7 (0.6)
SBP (mmHg)	BDC−7	129.5 (10.0)	125.4 (10.0)	129.7 (8.6)	127.6 (9.6)
	R+10	112.5 (7.8)	122.4 (7.0)	124.2 (9.3)	126.6 (8.1)
DBP (mmHg)	BDC−7	70.5 (7.5)	76.6 (7.1)	76.0 (8.6)	81.6 (9.6)
	R+10	66.5 (4.8)	77.6 (7.5)	72.7 (10.0)	81.0 (5.4)
TPR (dyn s cm^5)	BDC−7	1148 (235)	1318 (249)	1154 (246)	1395 (209)
	R+10	1026 (226)	1379 (182)	1223 (299)	1559 (188)
EDR (Hz)	BDC−7	0.27 (0.03)	0.29 (0.03)	0.27 (0.04)	0.27 (0.03)
	R+10	0.27 (0.02)	0.27 (0.03)	0.27 (0.03)	0.27 (0.02)
RRI:					
log HF (log ms^2)	BDC−7	2.85 (0.50)	2.38 (0.50)	2.58 (0.38)	2.40 (0.25)
	R+10	2.81 (0.49)	2.69 (0.45)	2.75 (0.47)	2.54 (0.34)
log LF (log ms^2)	BDC−7	3.10 (0.40)	3.02 (0.31)	3.03 (0.28)	3.09 (0.34)
	R+10	3.15 (0.29)	3.08 (0.28)	3.14 (0.21)	3.17 (0.25)
log VLF (log ms^2)	BDC−7	3.18 (0.39)	3.22 (0.37)	3.09 (0.35)	2.97 (0.21)
	R+10	3.34 (0.40)	3.30 (0.45)	3.22 (0.40)	3.15 (0.31)
log LF/HF	BDC−7	0.46 (0.07)	0.65 (0.48)	0.39 (0.05)	0.70 (0.29)
	R+10	0.34 (0.36)	0.39 (0.45)	0.38 (0.32)	0.63 (0.30)
DFA1	BDC−7	0.81 (0.15)	1.09 (0.20)	0.87 (0.16)	1.04 (0.11)
	R+10	0.90 (0.12)	0.96 (0.16)	0.89 (0.15)	1.03 (0.11)
DBP:					
log LF (log mmHg^2)	BDC−7	1.28 (0.25)	1.20 (0.33)	1.32 (0.23)	1.21 (0.14)
	R+10	1.43 (0.19)	1.26 (0.29)	1.28 (0.19)	1.26 (0.15)

hemodynamic variables) and **Table 3** (i.e., factors significance based on linear mixed models). The HR *delta score* of the CTRL group in supine position was positive and significantly higher than in sitting position (**Figure 4A**), suggesting that bed rest increased HR more in the supine than the sitting position in the CTRL group. The factor Group and its interaction with Posture were significant (**Table 3**), and bed rest did not increase HR in the TRAIN group (*delta scores* were negative). A significantly different *delta score* between groups in the supine position was also found. Bed rest decreased SV in both groups (**Figure 4B**), independent of posture (**Table 3**). CO (the product of HR and SV) reflected the combination of HR and SV *delta scores*. Both factors and their interaction were significant (**Table 3**) and *delta scores* differed between the groups in the supine position and between positions in the CTRL group (**Figure 4C**).

The factors Posture, Group, and their interaction were also significant for TPR (**Table 3**). The negative TPR *delta score* of CTRL participants in the supine position indicates that bed rest decreased supine TPR only in the CTRL group (**Figure 4D**). Posture and its interaction with Group were also significant factors for SBP (**Table 3**). Bed rest decreased SBP more in supine than in sitting position and markedly more in the CTRL group (**Figure 4E**). Effects of bed rest were less pronounced on DBP (**Figure 4F**) than on SBP.

Autonomic Response to the Postural Test

The shift from supine to sitting position was associated with an increase in the LF/HF powers ratio and DFA1, and a decrease in the HF power of RRI and the LF power of DBP—both before and after bed rest (**Table 2**). However, the prolonged bed rest period influenced these changes differently in the two groups (**Figure 5**). In fact, after bed rest, the HF power of RRI in supine position only increased in the TRAIN group (**Figure 5A**), and the DFA1 in sitting position only decreased in the CTRL group (with differences in *delta scores* between positions found only in the CTRL group, **Figure 5D**). Furthermore, bed rest decreased the sitting LF/HF index in CTRL participants only and influenced the supine LF power of DBP differently between groups (i.e., the *delta score* was positive for CTRL participants and negative for TRAIN participants, **Figures 5B** and **5C**).

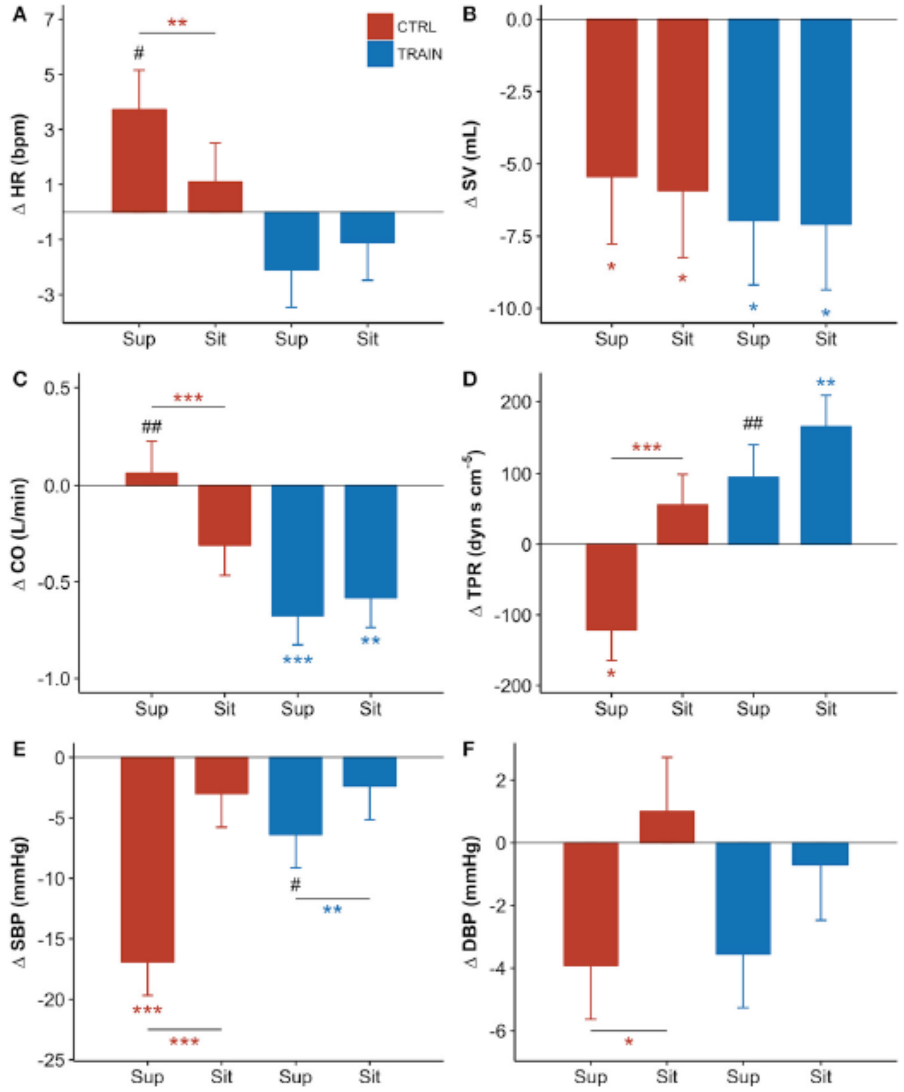

FIGURE 4 | (A–F) Delta scores of hemodynamic variables, i.e., the difference (Δ) between the value measured before bed rest (at BDC–7) and the corresponding value measured after bed rest (at R+10, see text) for the supine (Sup) and the sitting (Sit) position: adjusted means ± SE. For each panel: control group (CTRL) red bars on the left-hand side, and training group (TRAIN) blue bars on the right-hand side. Asterisks above whiskers indicate *delta scores* significantly different from zero. Horizontal lines with asterisks indicate significant differences between supine and sitting *delta scores* within the same group. Pound signs indicate significant differences between groups at the same position. **(A)** HR, Heart Rate; **(B)** SV, Stroke Volume; **(C)** CO, Cardiac Output; **(D)** TPR, Total Peripheral Resistance; **(E)** SBP, Systolic Blood Pressure; **(F)** DBP, Diastolic Blood Pressure. $^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#}p < 0.05$.

DISCUSSION

Our study investigated the alterations induced by 60 days of HDT in hemodynamics and autonomic modulations of heart rate. To the best of our knowledge, this study involved the highest number of participants to investigate these specific effects during long-term HDT bed rest so far. Our main findings show that: (1) HR progressively increased some days after the start of the HDT; (2) changes in SV and HR vagal modulations appeared almost synchronously; and (3) alterations in these variables and SBP were detectable several days after the end of bed rest, indicating persistent cardiovascular deconditioning. Furthermore, this high-intensity/short-duration exercise alleviated the cardiovascular deconditioning, counteracting the autonomic alterations and improving recovery. Although the adopted exercise protocol mainly involved the lower part of the body, it likely influenced central mechanisms of cardiac modulation and appears to be a promising countermeasure for long-term spaceflight missions. Different exercise-based countermeasures have been tested so far to reduce cardiovascular deconditioning. A previous study showed that low-magnitude whole body vibration with

TABLE 3 | Postural test: significance of Group and Posture factors and their interaction based on linear mixed models analysis (see text for abbreviations).

	Significance p		
	Group	**Posture**	**Group x Posture**
HR	<0.05	0.16	<0.01
SV	0.66	0.82	0.89
CO	<0.05	0.053	<0.01
SBP	0.16	<0.001	<0.001
DBP	0.76	<0.01	0.38
TPR	<0.05	<0.001	<0.05
RRI SPECTRAL POWERS:			
log HF	0.96	<0.01	<0.001
log LF	0.55	0.83	0.48
log VLF	0.99	0.26	0.23
log LF/HF	0.12	0.07	0.46
DFA1	0.48	<0.001	<0.001
DBP SPECTRAL POWERS:			
log LF	0.13	0.09	<0.001

resistive exercise prevented the increase of the autonomic index of cardiac sympathovagal balance after an HDT period lasting 60 days (as was the case in our study) without, however, improving orthostatic tolerance (Coupé et al., 2011). Other studies were different from the present in their design and duration. Nonetheless, these studies highlight the crucial role of exercise as a countermeasure against cardiovascular deconditioning. The intermittent exposure to hypergravity coupled with ergometric exercise limited the decrease in parasympathetic activity after 14 days of HDT (Iwasaki et al., 2005). Daily rowing ergometry and biweekly strength exercise training after 5 weeks of HDT prevented orthostatic intolerance only when combined with volume loading (Hastings et al., 2012). Finally, supine cycling could counteract orthostatic intolerance after 18-day bed rest only in combination with plasma volume restoration (Shibata et al., 2010). However, the vast range of different study designs and countermeasures complicate a direct comparison with the sledge jump training protocol.

Time Course of Hemodynamic Variables and Autonomic Indices During HDT

We described the time course of long-term HDT adaptations by comparing values during HDT with baseline measures in the supine position (0 degrees). Compared to sitting, the recumbent position is characterized by a fluid shift to the upper body, which increases stroke volume and stimulates baroreceptors and volume receptors, inducing cardiac vagal activation. By choosing this reference we could describe the isolated effect of the prolonged −6 degrees bed rest and this makes our results comparable with the cardiovascular changes observed during mid- and long-term spaceflight (Baevsky et al., 2007; Di Rienzo et al., 2008; Demontis et al., 2017). In the CTRL group, HR significantly increased from baseline starting from the 28th day of HDT and remained higher than baseline on the 56th day, in the recovery phase, and 10 days after the end of bed rest (R+10 supine; **Figure 2A**). A similar pattern was observed in another 60-day HDT study (Liu et al., 2015). Interestingly, this pattern was missing in the TRAIN group, where HR remained stable during and after HDT. The HR increase is a crucial feature of cardiovascular deconditioning, and the lack of this feature in the TRAIN group is a clear marker of the efficacy of the proposed training protocol as a cardiovascular countermeasure. A question arises about the type of training we adopted as short duration HIIT is not usually considered to act as a *vagal enhancer*. However, some data confirm that also this type of training may induce a parasympathetic adaptation of HR when performed in the supine position (Kiviniemi et al., 2014). An alternative hypothesis for the unchanged HR in TRAIN group after 28 days of bed rest might be constant increments in left atrial volume that could have induced a bradycardic response by stretching the sinus node. However, this unlikely occurred in our study because we found a significant reduction in SV in both groups (**Figure 2A**). SV depends on contractility, on arterial blood pressure, and on atrial pressure. Since contractility did not change (as sympathetic indices of HRV remained stable in the TRAIN group) and arterial blood pressure did not change from HTD28 onwards, we may hypothesize that atrial pressure, although not directly measured, was chronically reduced (perhaps via reduced blood volume and hence preload) in both groups of subjects. A previous echocardiographic study during bed rest confirmed that the left ventricular end-diastolic volume (a surrogate of cardiac preload) progressively decreases throughout 60 days of bed rest (Westby et al., 2016). Hence, it appears that the main reason for the unchanged HR in the trained subjects could be a training-induced enhancement of vagal tone. SV progressively decreased in both groups during HDT, reaching a minimum at the end of bed rest (i.e., about 90% of the baseline value). The SV reduction is in line with the literature on HDT, which reports a decrease in plasma and blood volume by 10 to 30% within the first 24 to 72 h of confinement (Convertino, 2007). A decrease in SV suggests a dehydration condition, which was probably due to different reasons. One factor was the increased renal sodium excretion and thus reduced water retention (Convertino, 2007). Another factor could be related to tissue compression in lying position that dehydrated areas of weight bearing because of greater interstitial flow into the microcirculation (Hargens and Vico, 2016). The reduced daily physical activity might also have been a cause of dehydration (Convertino, 2007).

The training not only failed in counteracting the decrease in SV, but it might have even accelerated it. On the 28th day of bed rest, SV was 92% of the baseline value in both groups, but on the 2nd day it was equal to 100% in CTRL participants and decreased to 91% in TRAIN participants. Moreover, on the 2nd day of bed rest SBP decreased significantly only in the TRAIN group, and DBP changes tended to be lower in the TRAIN when compared to the CTRL group (**Figures 2E** and **2F**). This contrast suggests that exercise training might quickly influence the hemodynamic balance, inducing post-exercise hypotension likely due to an early blood volume reduction. We speculate that training might accelerate the loss of plasma

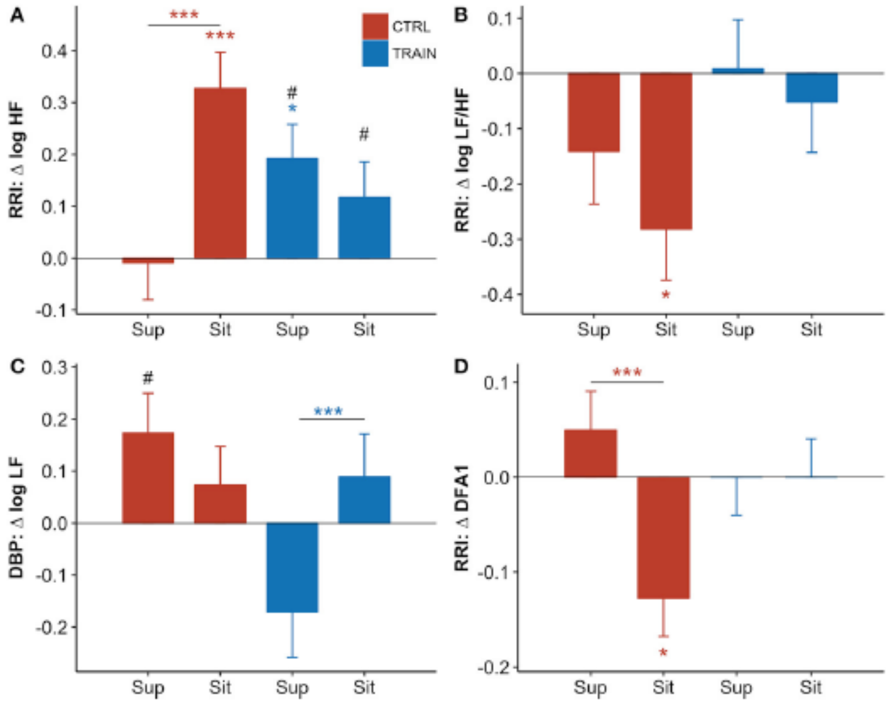

FIGURE 5 | (A–D) Delta scores of autonomic variables, i.e., the difference (Δ) between the value measured before bed rest (at BDC−7) and the corresponding value measured after bed rest (at R+10, see text) for the supine (Sup) and the sitting (Sit) position: adjusted means ± SE. For each panel: control group (CTRL) red bars on the left-hand side, and training group (TRAIN) blue bars on the right-hand side. Asterisks above whiskers indicate *delta scores* significantly different from zero. Horizontal lines with asterisks indicate significant differences between supine and sitting *delta scores* within the same group. Pound signs indicate significant differences between groups at the same position. RRI, R-R intervals; **(A)** HF, High-Frequency power; **(B)** LF/HF, Low-Frequency to High-Frequency powers ratio; **(C)** LF, Low-Frequency power; **(D)** DFA1, short-term fractal index by detrended fluctuations analysis. $^{***}p < 0.001$, $^{*}p < 0.05$, $^{\#}p < 0.05$.

volume, as demonstrated by recent works showing that lower limb exercise (cycling) produced a different adaptation of the autonomic sympathetic tone in supine vs. upright position (Ried-Larsen et al., 2017). Supine position activated the stretch receptors of heart, veins, and pulmonary circulation, increasing central blood volume, and blunting the metaboreflex activation. Such a response reduced heart contractility, limiting SV, and reducing blood pressure via a non-renal mechanism. At the same time, this reaction could be responsible for a reduction in plasma renin activity and therefore for an early increase in water loss (Ried-Larsen et al., 2017). Thus, a potential additive effect on the cardiovascular system of acute blood volume changes and sympathetic response to exercise might occur in the first days of training and HDT. We can suggest that, in order to prevent such additive effect, the exercise-based countermeasures should start at full load a few days after exposure to microgravity or its analog. The only other time point at which we observed a significant difference in blood pressure between groups was 10 days after the end of HDT (R+10), when CTRL participants showed a decrease in supine SBP compared to baseline of 17 mmHg (see **Table 2**), a marked phenomenon of hypotension absent in the TRAIN group. As will be discussed later, this suggested that prolonged bed rest had long-term effects on blood pressure control mechanisms, potentially leading to orthostatic hypotension at the restoration of normal gravity conditions. The implemented training protocol showed positive effects on these cardiovascular modifications. With respect to the cardiac autonomic modulations of HR, previous studies documented a decrease in HRV total power and vagal indices in early and chronic HDT (Fortrat et al., 1998; Sigaudo et al., 1998; Pavy-Le Traon et al., 2007), as well as contrasting findings on the sympathetic cardiovascular control (Hughson et al., 1994; Sigaudo et al., 1998; Fortrat et al., 2001; Ferretti et al., 2009). In our study, the HF power decreased significantly in the CTRL group on the 28th and 56th day of bed rest (**Figure 3**). The breathing rate was stable before, during, and after HDT, always falling within the HF band (**Table 2**). In our experimental set-up, the HF power thus correctly represented the respiratory component of the parasympathetic modulations of HR. Therefore, our data indicated that HDT induced a substantial reduction in vagal modulations of HR in the respiratory band. The LF/HF powers ratio is an index of cardiac sympathovagal balance: in the CTRL group, it tended to increase on the 28th and 56th day (+9 and +13% after log transformation, **Figure 3F**). Additionally, DFA1 quantifies changes in the sympathovagal balance, but unlike the LF/HF powers ratio, it considers fractal components of the HR dynamics not related to the amplitude of the oscillations. Concurrently with the HF power reductions (**Figure 3A**), DFA1 also tended to increase in the CTRL group on the 28th and 56th day of bed rest and remained higher than baseline even 10 days (i.e., R+10) after the end of bed rest (**Figure 3D**). The LF power reflects both the vagal and sympathetic cardiac modulations; in CTRL participants it decreased in a similar fashion as the HF power, suggesting the predominance of the vagal withdrawal compared to possible sympathetic activation (**Figure 3B**). The VLF power reflects the cardiac modulations of different humoral and thermoregulatory mechanisms superimposed on the autonomic cardiac control; the time course of the VLF power during bed rest was remarkably similar in the two groups, suggesting that the effects of training on the changes in HR variability during bed rest mainly regards the fast-vagal modulations of HR (**Figure 3C**). Unlike DFA1 or the LF/HF powers ratio, the power of DBP oscillations in the LF band is a measure of sympathetic vascular control not influenced by parasympathetic modulations. This index did not show any significant effect of bed rest (**Figure 3E**). Therefore, the analysis of changes occurring during bed rest in the cardiovascular autonomic indices suggested a reduction of vagal heart rate modulations and an increase in the sympathovagal balance without evidence of an altered sympathetic tone in the CTRL group. This effect was detectable up to 10 days after the end of bed rest. The trends were different in the TRAIN group without apparent alterations during the HDT period with regard to any autonomic index. Therefore, our results suggested that during HDT the reactive jumps training reduced the cardiac autonomic deconditioning.

Hemodynamic and Autonomic Response to the Postural Test

The postural test allowed for the evaluation of the effects of the 60-day HDT on the cardiovascular system as it operates around different working points. In the supine position, the upper part of the body contains a larger volume of fluids than in sitting position. The fluid shift from sitting to supine posture is expected to increase the volume of the large vessels and the filling of the heart chambers, stimulating volume receptors which induce an autonomic response. The descriptive statistics of hemodynamic variables and autonomic indices in **Table 2** showed higher SV and vagal index, and lower HR, sympatho/vagal balance indices, and TPR in supine compared to a sitting position. Our results indicate that in the recovery phase 10 days after bed rest, the cardiovascular deconditioning affects some variables more in one position than in the other. For instance, this is the case with HR (**Figure 4A**) because the HR *delta score* of the CTRL group significantly differed from zero in only the supine position. Such a finding points out that after HDT without countermeasures, the cardiovascular deconditioning affects HR more in supine than in sitting position. HR *delta scores* of TRAIN participants were indeed closer to zero in both positions and lower than those of the CTRL group in the supine position (**Figure 4A**). This finding confirms the efficacy of the administered training protocol as a countermeasure for cardiovascular deconditioning. In contrast to HR, SV showed the same significant reduction in the recovery phase, between −5 and −7 mL, independent of the posture in both groups, suggesting that the training protocol did not affect the loss of body fluids caused by HDT. Interestingly, the postural test was able to detect a significant reduction in TPR in the CTRL group (**Figure 4D**), but in the supine position only. The difference between the two postures was also highly significant in the CTRL group. It is possible that the fall in supine TPR induced by the 60-day HDT was responsible for the significant reduction in supine SBP observed at R+10 only in the CTRL group (**Figure 2E**)—a hypotensive effect also evidenced by the negative *delta score* of supine SBP (**Figure 4E**). The significant differences between supine and sitting *delta scores* of TPR, SBP, and DBP in CTRL participants further highlighted that long-term effects of head-down-tilt bed rest depended on posture. In this regard, the crucial point is that the sledge jump training protocol showed positive effects. No significant *delta scores* were observed in the TRAIN group for TPR and BP in the supine position, indicating the ability of the administered training protocol to accelerate recovery after HDT bed rest. Interestingly, in the TRAIN group the significantly positive *delta score* of TPR in sitting position (**Figure 4D**) indicates that exercise training might even have improved the capability to increase the total peripheral resistance in sitting position. An improved endothelial function induced by training (Ashor et al., 2015) could mediate such an effect. The autonomic indices (**Figure 5**) also shows the effects of HDT related to the posture. When sitting in the recovery phase, the CTRL group had lower sympathovagal activation and vagal withdrawal (**Table 2**). This is demonstrated statistically by significant negative *delta scores* of the LF/HF powers ratio and DFA1 and by a significant positive *delta score* of the HF power in sitting position (**Figure 5**). This phenomenon, suggests an impaired autonomic response to a postural shift after prolonged bed rest, a possible marker of orthostatic intolerance. By contrast, the TRAIN group had unchanged (i.e., null) *delta scores* for the indices of sympathovagal balance in both supine and sitting positions, whereas the index of vagal modulations of HR (HF power, **Figure 5A**) increased after bed rest in a similar manner for both postures. These findings therefore suggest that the proposed training protocol allowed for a faster recovery of the physiological autonomic responses to posture changes.

CONCLUSION

Considering that a supine position on Earth mimics acute cardiovascular effects of weightlessness, which induces a robust vagal activation immediately after the fluid shift to the upper body, we described the time course of long-term changes by comparing HDT to supine baseline recordings. Our data revealed different dynamics of cardiovascular adaptations. The acute autonomic changes induced by the supine position persisted throughout short-term HDT exposure and were strongly attenuated during mid-term and long-term HDT exposure, whereas SV adaptations showed an enduring trend. The administered training protocol appeared to mitigate some of the autonomic cardiovascular adaptations occurring during mid- or long-term HDT exposure and to accelerate their recovery after bed rest. The hypotensive phenomenon observed in the TRAIN group only during short-term HDT exposure, however, suggests that administering this exercise with initially light but progressively heavier loads during the first days of bed rest is an effective countermeasure.

AUTHOR CONTRIBUTIONS

MM, PC and AS wrote the manuscript and processed the data. AS designed and directed the project. KB helped supervise the project and performed data collections with support from AW and SM. PC and MM preprocessed data for statistical analyses. AS performed statistical analyses and prepared the figures and tables. PC, MM, GM, and AS drafted the manuscript. H-CG, LR, MS, and OO provided critical feedback and contributed to the interpretation of the results. All authors discussed the results and contributed to the final manuscript.

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2.4 Fourth paper. The *trained heart*: HRV and performance in extreme environment

Rundfeldt LC* and **Maggioni MA***, Coker RH, Gunga HC, Riveros-Rivera A, Schalt A, Steinach M. (2018) *Cardiac Autonomic Modulations and Psychological Correlates in the Yukon Arctic Ultra: The Longest and the Coldest Ultramarathon.* *These Authors contributed equally, Front. Physiol. 9, 35.

This work analyses the heart response during a unique long-duration performance in extreme cold and wild environment as for cardiac autonomic modulations, with two different purposes: 1) to explore the use of HRV to monitor/predict the performance in this specific setting, and 2) to evaluate HRV analysis as a tool to assess also performance's psychological correlates.

15-min HR recordings with an heart rate monitor were collected in lying position, resting, at morning, upon awakening in n=16 competitors (12 men, 4 women) of a long subarctic ultramarathon race, the Montane® YAU (Yukon Arctic Ultra), 690 km-long, with ambient temperatures ranging between +5 °C and -47 °C. Data were collected before the race, during the race, i.e., after 277 km at the first checkpoint (D1), and after 383 km (D2) at the second checkpoint, and on the morning immediately after the end of the race. In the same experimental sessions psychometric scales were administrated, as Profile of Mood State (POMS), Karolinska Sleepiness Scale (KSS) and Borg Total Quality Recovery (TQR) scale. Upon arrival to the checkpoints (and to the finish line), the Borg Rate Perceived Exertion (RPE) scale was also conducted.

Participants who interrupted the race were pooled in the *non-finishers* group (NON, n = 6), whereas those who completed the racetrack were pooled in the *finishers group* (FIN, n = 10), to compare performance characteristics and baseline data.

During the race, HR was significantly higher with respect to baseline in both groups, reaching the highest value at D1 and then showing in FIN a trend to decrease, still not returning to pre-race values in the morning after the end of the race. The HR increase was associated to a parasympathetic withdraw, showed by depressed HRV vagal indices in time domain, i.e., the number of NN intervals in one hour that are >50 ms (NN50+) or < 50 ms (NN50–). However, in FIN group only, baseline HR was negatively correlated to mean velocity: the lower the baseline resting HR (thus the higher the vagal tone), the higher the mean velocity (i.e., better performance). POMS scale reflected the race burden: *Vigor* decreased, and *Fatigue* increased, both significantly. No appreciable differences were retrieved regarding the other psychometric scales.

In conclusion, we observed the expected vagal depression during the race; however, successful runners could mitigate and better restore it. In line with literature data, lower HR and higher vagal tone before the race predicted a better performance. The POMS scale may be useful to assess psychological correlates and seems consistent with HRV results, therefore POMS, HR and HRV could be informative and valuable tools to monitor/predict physical performance in this specific setting.

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Cardiac Autonomic Modulations and Psychological Correlates in the Yukon Arctic Ultra: The Longest and the Coldest Ultramarathon

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Studies on human physical performance in extreme environments have effectively approached the investigation of adaptation mechanisms and their physiological limits. As scientific interest in the interplay between physiological and psychological aspects of performance is growing, we aimed to investigate cardiac autonomic control, by means of heart rate variability, and psychological correlates, in competitors of a subarctic ultramarathon, taking place over a 690 km course (temperatures between +5 and −47°C). At baseline (PRE), after 277 km (D1), 383 km (D2), and post-race (POST, 690 km), heart rate (HR) recordings (supine, 15 min), psychometric measurements (Profile of Mood States/POMS, Borg fatigue, and Karolinska Sleepiness Scale scores both upon arrival and departure) were obtained in 16 competitors (12 men, 4 women, 38.6 ± 9.5 years). As not all participants reached the finish line, comparison of finishers (FIN, $n = 10$) and non-finishers (NON, $n = 6$), allowed differential assessment of performance. Resting HR increased overall significantly at D1 (FIN +15.9; NON +14.0 bpm), due to a significant decrease in parasympathetic drive. This decrease was in FIN only partially recovered toward POST. In FIN only, baseline HR was negatively correlated with mean velocity [r −0.63 (P.04)] and parasympathetic drive [pNN50+: r −0.67 (P.03)], a lower HR and a higher vagal tone predicting a better performance. Moreover, in FIN, a persistent increase of the long-term self-similarity coefficient, assessed by detrended fluctuation analysis (DFAα2), was retrieved, possibly due to higher alertness. As for psychometrics, at D1, POMS Vigor decreased (FIN: −7.0; NON: −3.8), while Fatigue augmented (FIN: +6.9; NON: +5.0). Sleepiness increased only in NON, while Borg scales did not exhibit changes. Baseline comparison of mood states with normative data for athletes displayed significantly higher positive mood in our athletes. Results show that: the race conditions induced early decreases in parasympathetic drive; the extent of vagal withdrawal, associated to the timing of its recovery, is crucial for success; pre-competition lower resting HR predicts a better performance; psychological profile is reliably depicted by POMS, but not by Borg fatigue scales. Therefore, assessment of heart rate variability and psychological profile may monitor and partly predict performance in long-duration ultramarathon in extreme cold environment.

Keywords: cold, exercise performance, extreme environments, fatigue, heart rate variability, mood, subarctic ultramarathon, ultra-endurance

INTRODUCTION

Human physiology is characterized by continuous reactive adaptation to internal and external conditions and stressors (Ramirez et al., 1999; Hawley et al., 2014). Subjects exposed to extreme conditions and environments display astounding adaptive potential, which ultimately ensures optimal adjustment to current organismic demands and external stress (Kälin et al., 2012; Gunga, 2014). Assessment of autonomic cardiac modulation by means of heart rate variability (HRV) has shown to be a reliable tool to evaluate not only physiological changes (Taralov et al., 2015; Kobayashi et al., 2016), but also psychological aspects of human reactive adaptation to different stressors (Souza et al., 2013). Therefore, HRV assessment may describe human resilience, as it represents a bridge between physiology and psychology, and, by integrating these two aspects, it mirrors human adaptive ability (Thayer et al., 2009; Spangler and Friedman, 2015). Particularly in endurance athletes, training effects, performance level and physical wellbeing may be contextualized through HRV assessment (Atlaoui et al., 2007; Plews et al., 2013a; Buchheit, 2014; Bellenger et al., 2016a). Successful adaptation to increased training load, resulting in improved performance, is associated with increased HRV, as well as enhanced parasympathetic predominance at rest (Plews et al., 2013b; Stanley et al., 2015; Lucini et al., 2017). Assessment of autonomic cardiac modulation conducted directly post-exercise or after competitions, demonstrated a decrease in HRV and a parasympathetic withdrawal (Bricout et al., 2010; Buchheit et al., 2010; Bellenger et al., 2016a), which, however, was effectively recovered depending on the intensity of the preceding exercise (Martinmäki and Rusko, 2008; Manzi et al., 2009; Stanley et al., 2015), and on the individual's training status (Bricout et al., 2010; Buchheit et al., 2010; Bellenger et al., 2016a). This has been vastly evidenced in endurance exercisers (Buchheit et al., 2010; Plews et al., 2012; Da Silva et al., 2014; Kiviniemi et al., 2014), and investigations of cardiac autonomic function in response to extreme endurance exercise, such as ultramarathon, display similar findings (Gratze et al., 2005; Scott et al., 2009; Foulds et al., 2014), even though specific studies related to cardiac autonomic modulation during ultramarathon, are still scarce in comparison. On the other hand, in ultra-endurance athletes, physical exertion has been commonly associated with mental fatigue and increased mood disturbance (Anglem et al., 2008; Siegl et al., 2017), especially in participants who experience adverse incidents, then perform poorly or are forced to prematurely withdraw (Parry et al., 2011; Joslin et al., 2014).

Ultramarathon is mostly defined by course lengths exceeding marathon distance and is characterized by the combination of extremely challenging highly intensive exercise (e.g., track lengths >300 km or great elevation gains), often under strenuous environmental conditions, with concurrently impaired possibilities to recover. The Yukon Arctic Ultra (YAU) is considered to be one of the world's toughest ultramarathons (Coker et al., 2017), as it combines the great course distance of 690 km with extreme environmental conditions typical of a subarctic winter. Except for several in-race checkpoints, there are no indoors sleeping vacancies, so that competitors have to camp on the race-course and experience complete environmental exposition. Therefore, YAU competitors are challenged by a *three-folded stress stimulus* of (i) long-term strenuous exercise, (ii) extreme cold exposure, and (iii) impaired resting conditions, due to in-race camping. So far, among studies on ultra-endurance exercise, research objectives mostly diverge from evaluation of autonomic cardiac function in ultramarathon runners (Degache et al., 2014; Hurdiel et al., 2015; Mrakic-Sposta et al., 2015; Wüthrich et al., 2015; Tonacci et al., 2017), which, to our knowledge, was only implemented in three previous studies (Gratze et al., 2005; Scott et al., 2009; Foulds et al., 2014). However, these investigations differed regarding (i) the race length (e.g., 160 km ultramarathon, or Ironman competition with a total distance of 226.35 km), (ii) study protocol (i.e., pre- vs. post-race comparison only), (iii) environmental conditions (mild climate, summer), and (iv) terrain characteristics (e.g., mountain, large altitude variation, etc.). Therefore, this is the first study to assess cardiac autonomic modulation in competitors of an extremely long (i.e., 690 km) ultramarathon on a mostly flat course, in subarctic climate, which may provide essential insights into the adaptive capacity, as, aside from exercise, HRV is associated with numerous external and internal factors (Rajendra Acharya et al., 2006; Shaffer et al., 2014).

With outdoor temperatures ranging from +5 to −47°C and the air humidity accounting for up to 100%, YAU competitors face extreme subarctic weather conditions. Comparable scientific knowledge is, however, insufficient. Autonomic balance has been observed to shift toward greater parasympathetic predominance during Antarctic stays (Farrace et al., 2003; Harinath et al., 2005), but these results were obtained in expeditioners confined to indoors housing. Moreover, a significant interplay between autonomic cardiac regulation and psychological wellbeing has been observed (Sakuragi et al., 2002; Karavidas et al., 2007; Sgoifo et al., 2015), so that psychometric assessment may also serve to contextualize findings about HRV (Bellenger et al., 2016b; Flatt et al., 2017b). Increased performance and greater parasympathetic drive in cardiac autonomic regulation are associated with increased psychological wellbeing (Cervantes Blásquez et al., 2009; Bisschoff et al., 2016). Conversely, fatigued states and increased mood disturbance have been related to decreased indexes of total HRV, as well as parasympathetic tone (Nuissier et al., 2007; Leti and Bricout, 2013; Schmitt et al., 2013; Flatt et al., 2017a). In this context, impaired resting conditions present another vital influence on cardiac autonomic regulation. Assessment under concurrent sleep-deprivation, which itself is again related to impaired both cognitive and physical performance (Marcora et al., 2009; Fullagar et al., 2015), shows decreased HRV indexes in the parasympathetic domain (Dettoni et al., 2012; Glos et al., 2014; Tobaldini et al., 2014).

To our knowledge, exposition to such a particular combination of stress-stimuli as presented by competition in the YAU has never been investigated regarding cardiac autonomic function and psychological profile. Therefore, we assessed autonomic cardiac regulation in terms of HR/HRV, as well as psychometric measurements including mood states, indicators of sleepiness, exertion and recovery, to investigate adaptation to extreme conditions and performance, by analyzing cardiac autonomic control and its interplay with mood and fatigue. We hypothesized that higher performing competitors, compared to less successful athletes, would exhibit differential profiles of autonomic cardiac regulation associated with optimal psychometric profile, overall characterized by higher adaptability and greater resilience to the extreme challenges of the three-folded stress stimulus.

MATERIALS AND METHODS

Subjects and Study Implementation

This study is part of a larger investigation regarding "*Physiological changes of participants of the Yukon Arctic Ultra - an ultramarathon in extremely cold climate*," where it is planned to assess a variety of different physiological parameters and their interplay.

From a total number of 78 athletes partaking in the 690 km foot-race category of the YAU during the years 2013, 2015, and 2017, 27 (20 men, 7 women) volunteers enrolled in the study (8 in 2013, 9 in 2015 and 10 in 2017). Due to issues related to data collection, from the 27 participants, only 16 (ALL: 12 men, 4 women) were included in the data analysis (see section Statistics). The majority ($n = 15$) were of Caucasian descent and one was of Asian origin. Their anthropometric data are presented in **Table 1**.

The recruitment for this study was conducted with the support of the event organizers. A call for participants, with a brief description of the study and planned measurements, was transmitted to the athletes who had enrolled in the 690 km foot-race category. The organizers were encouraged to predominantly contact experienced athletes, who had a long history of completed endurance events and/or who had completed the YAU before. Athletes who were interested in the study contacted the principal investigator via e-mail and received further detailed information. The potential study participants had several weeks to ask questions via e-mail and to decide whether to partake in the study or not. There were no further inclusion or exclusion criteria: all athletes enrolled in the 690 km foot-race category were eligible to enter the study. All athletes were required to present to the event organizers a health certificate issued by their home physician, in order to be enrolled in the race. During a meeting in Whitehorse, Yukon Territory, Canada, 4–5 days before the race start, the potential study participants met with the investigators in person, had the chance to ask further questions and to finally give their informed written consent to partake in the study. The study was approved by the Charité Ethics Board (review number EA4/109/12), and all measurements and procedures complied with the Declaration of Helsinki (54th Revision 2008, Korea)[1] regarding the treatment of human subjects.

TABLE 1 | Subject demographics.

Group	Gender	*n*	Age, years mean (S.D.)	Weight, kg mean (S.D.)	Height, cm mean (S.D.)	BMI, kg/m^2 mean (S.D.)
FIN	Men	7	42 (10)	80 (9)	176 (6)	25.7 (3.0)
	Women	3	38 (10)	61 (2)	168 (10)	21.7 (3.4)
	All	10	40 (9)	74 (12)	174 (8)	24.5 (3.5)
NON	Men	5	33 (7)	79 (12)	179 (10)	24.7 (1.7)
	Women	1	51 (0)	58 (0)	170 (0)	20.1 (0)
	All	6	36 (10)	76 (14)	177 (10)	23.9 (2.4)
ALL	Men	12	38 (10)	80 (10)	177 (7)	25.2 (2.5)
	Women	4	41 (11)	60 (2)	169 (9)	21.3 (2.9)
	All	16	39 (10)	75 (12)	175 (8)	24.3 (3.1)

Subject demographics at baseline for all participants (ALL) and in subgroups (FIN and NON). No significant differences between groups.

All study participants included in the final analysis had completed either one marathon (9.6 ± 24.4) or ultramarathon (14.4 ± 24) prior to their study-participation. The mean longest ultramarathon distance completed by the athletes before their YAU participation was 380 ± 220 km. In addition, seven of the study participants had previously participated in the YAU foot-race in various distance categories, with a mean longest completed distance of 478 ± 219 km. Thus, the study participants were experienced endurance athletes, which is also reflected by their self-reported sedentary HR of 52.6 ± 7.3 bpm. From one participant, this background data was not made available.

The Yukon Arctic Ultra: The Longest, the Coldest Ultramarathon

The Montane® YAU ultra-endurance race takes part in the beginning of February, covering a 690 km distance between Whitehorse and Dawson City in the Canadian Yukon Territory. Besides the foot-race, the YAU also allows the competition in cross-country-skiing and mountain-biking. The first and last sections of the trail account for elevations between 500 and 700 m, however, especially in the last 200 km, the terrain along the Yukon river partly exhibits great elevation gains (up to 1,000 m). The YAU is not an orientation race, as the trail is marked and prepared with snow-mobiles. Via GPS devices, athletes can be tracked on the course and have the possibility to call for assistance in case of an emergency. To

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[1] https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

further increase their safety, the time until the race has to be completed is limited to 14 days and additionally, medical screenings are administered at the 10 checkpoints which are located (mostly about 50 km apart) along the route. Despite these partly indoor vacancies (otherwise, tents were provided), during the race, competitors face complete exposition to the subarctic environment, with outdoor temperatures in February ranging between +5°C (highest temperature measured in February 2013 in Whitehorse) and −47°C (lowest temperature measured in February 2015 in Dawson City). Additionally, the extremely high air humidity (up to 100% as measured in February 2013 in Whitehorse) contributes to the possible onset of frostbite, which, along with other (medical) concerns, may lead to immediate disqualification. Importantly, the weather conditions between editions were not significantly different (**Figure 1**), detailed information on weather conditions can be assessed in respective weather archives[2].

Notably, participants walked between 12 and 15 h per day whilst pulling their gear on a sled-like pulk (accounting for 30–40 kg; additionally, participants were allowed up to three drop bags) and, apart from the checkpoints, had to eat, rest and make toiletry arrangements in the outdoor conditions of the Yukon Territory.

More detailed information about the Montane® YAU is provided on the official website of the event[3].

Experimental Protocol and Measurements

Experimental protocol details are depicted in **Figure 2**. At two out of ten in-race checkpoints, we respectively implemented two in-race assessments, so that, in summary, measurements were performed: (1) at baseline during the 3 days preceding the race in Whitehorse (PRE), (2) at the Carmacks in-race checkpoint at 277 km (During 1, D1), (3) at the Pelly Crossing in-race checkpoint at 383 km (During, D2) and (4) immediately after completion of the race in Dawson City at 690 km (POST).

The in-race checkpoints had to be selected for measurement implementation due to essential practical concerns. They had to be indoors facilities buildings with sufficient space, comfortable ambient temperature and low noise in order to perform measurements under controlled conditions, as well available electricity and that it was accessible by car for the investigators. Exemplarily, several of the race checkpoints were mere tents that did not meet these criteria and therefore, the study checkpoints were chosen as they were. Thus, the distance between the race start (i.e., PRE) and the first in-race assessment (D1) accounted for over a third (277 km) of the entire race-course and additionally, in this period, athletes would face the most strenuous weather conditions (which tend to ameliorate toward the second half of the month; see **Figure 1**). As the second assessment was performed at 383 km (D2), the distance between D1 and D2 (as well as the time to cover it, which accounted for only 30 h in some subjects) was the shortest between the measurements and, in fact, more than 50% less than the other two distances. Conversely, the distance between D2 and POST was again very high (307 km) and additionally, the terrain in the last third of the course accounted for the greatest elevation gains (see section The Yukon Arctic Ultra: The Longest, the Coldest Ultramarathon).

Baseline Assessment

During the three race-preceding days (PRE), baseline anthropometric data (age, weight and height) were obtained. Weight was measured using a calibrated scale (Seca® GmbH, Hamburg, Germany) and height was taken from the participants' interview.

Fifteen minutes baseline recordings of beat-to-beat HR to assess HRV were collected with a HR monitor (RS800CX Polar Electro Oy, Kempele, Finland), which is widely used and validated for HRV assessment (Wallén et al., 2012). HR recordings were performed in supine position upon awakening (between 5 and 10 a.m.) directly after participants had slept 6–8 h the previous night. The athletes had not consumed food, beverages or stimulants (e.g., coffee) in the 2 h before the recording and were instructed to breathe normally, avoid speaking and moving during the data collection. Additionally, it was ensured by the investigators that subjects would not fall asleep. With the limitations of this specific in-field study, special attention was devoted to performing data collection sessions in a quiet and comfortable setting, with participants lying in a bed or on a sleeping sleeping mattress, ambient temperatures between 17 and 23°C, and reduced light.

On the morning of the race start before departure, additionally, psychometric assessment was performed (see **Figure 2** and section Psychometric Assessment).

In-Race and POST Assessment

Upon arrival at the in-race checkpoints, as well as at the race finish, psychometric scales were administered according to physiological needs and conditions of arriving competitors. Participants then had a few hours of rest (ranging from 4 up to 6–8 h) and upon awakening (at morning, between 5 and 10 a.m.), HR data was collected, as at baseline, to assess HRV. Afterwards, before departure, psychometric assessment again took place (see **Figure 2** and section Psychometric Assessment).

Indoors ambient conditions between the different measurement facilities were comparable, with special attention dedicated to a quiet and comfortably warm setting with reduced light exposure.

Moreover, throughout the entire race, participants were continuously (day and night) monitored by means of a heart rate monitor (RS800CX Polar Electro Oy, Kempele, Finland - sample rate 15 s).

Data Analysis

Performance Assessment and Heart Rate Continuous Recordings

The official time at the end of the race for each participant who reached the finish line was collected, together with the times and the respectively completed distance for each participant who had to withdraw. Subsequently, the mean running velocity of the race

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[2] http://climate.weather.gc.ca/historical_data/search_historic_data_e.html.

[3] http://arcticultra.de/en.

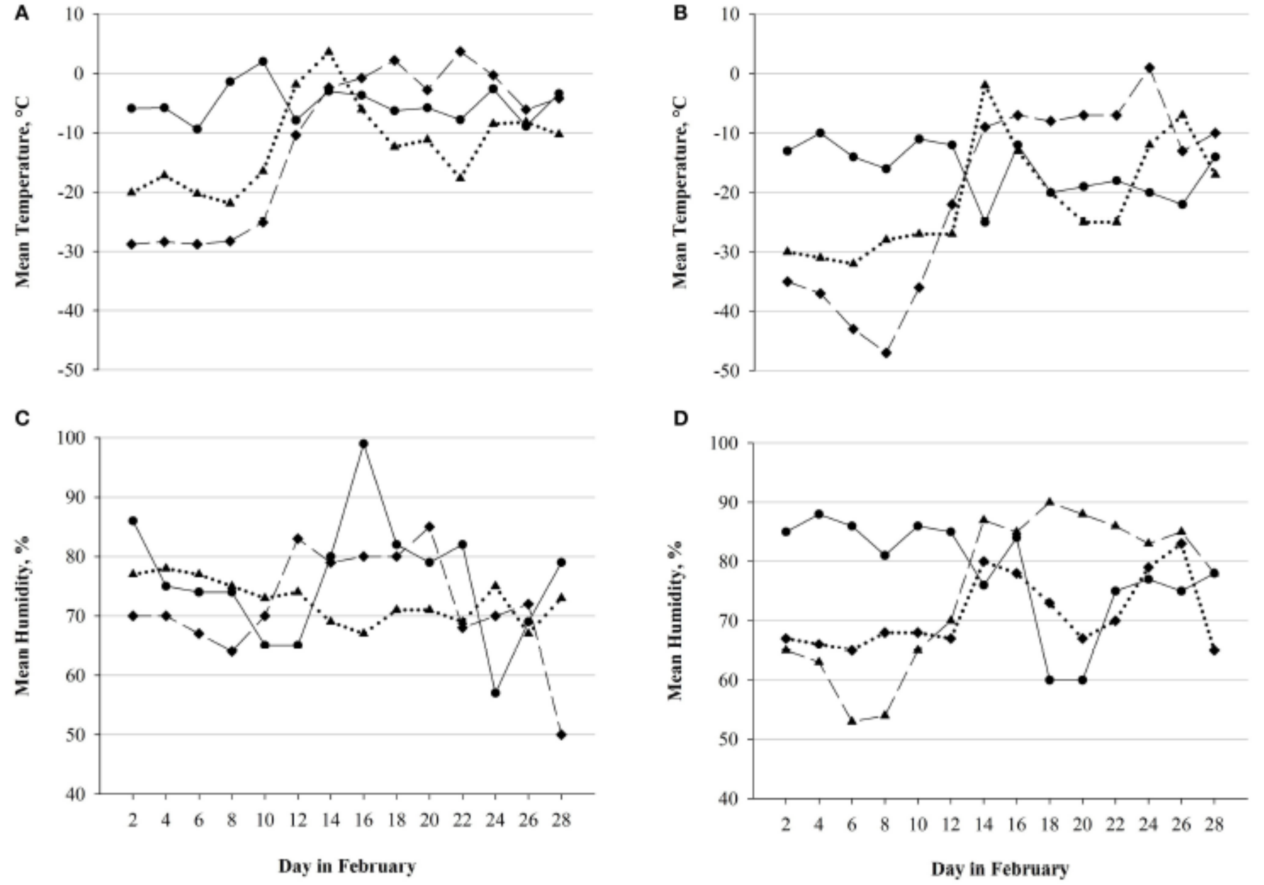

FIGURE 1 | Weather conditions across editions. Mean temperature and mean humidity as measured in Whitehorse and Dawson City in February 2013 (solid line), February 2015 (long dashed line), and February 2017 (dotted line). **(A)** Mean temperature in Whitehorse. **(B)** Mean temperature in Dawson City. **(C)** Mean humidity in Whitehorse. **(D)** Mean humidity in Dawson City. No significant differences between editions or locations[4].

was calculated from the total recorded time and the total distance covered $[\textit{time}\ (h)/\textit{space}\ (km) = \textit{velocity}\ (km/h)]$. By collection of in- and out-going times at in-race measurement points for each participant, both split times and velocities could be computed, allowing detailed assessment of performance. Additionally, continuous HR measurements served to determine exercise intensity, as well as resting quality (in respect to HR expressed as a percentage of calculated maximal HR). The continuous HR recordings, collected during the race, were screened for quality (no more than 3% signal lost/disturbed). The average, maximum and minimum HR were determined per each selected race period, and the values were normalized with respect to the individual age-related maximal HR (HR_{max}) (Tanaka et al., 2001). This provided further information about exercise intensity and quality of rest. Specifically, data were divided into four time-segments, according to the selected period of recording: (i) HR recorded in the first 36 h following the race start (D1a), (ii) during the 24 h before arriving at D1 (D1b), (iii) during the 24 h before arriving at D2 (D2a), and (iv) HR recorded during the last 24 h before finishing the race (D2b). Collected HR data were then expressed as a percentage of the HR_{max}, for average exercise intensity (ExHR) and average resting HR (RestHR). This approach was selected to allow comparison with parameters assessed at checkpoints (i.e., psychometric and HRV analysis) and, by classifying data, served to better interpret findings.

Heart Rate Variability Assessment

An expert operator visually inspected the R–R interval series, and with the support of a dedicated software (Kubios HRV ver. 2.1, Kuopio, Finland), premature beats or artifacts were removed. The filter threshold was set at the "low" level (Tarvainen et al., 2014) and only files 15-min long and including less than 0.3% of beats recognized as artifacts were considered; then the last 10 min were selected for HRV assessment, to better standardize the analysis. After providing the normal-to-normal (NN) interval series, HRV was assessed as validated indices of autonomic cardiac modulation, based on time-domain, frequency-domain,

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[4] Data taken from https://www.timeanddate.com/weather/canada/whitehorse/historic, https://www.timeanddate.com/weather/canada/dawson-city/historic and http://climate.weather.gc.ca/historical_data/search_historic_data_e.html (last accessed December 13, 2017).

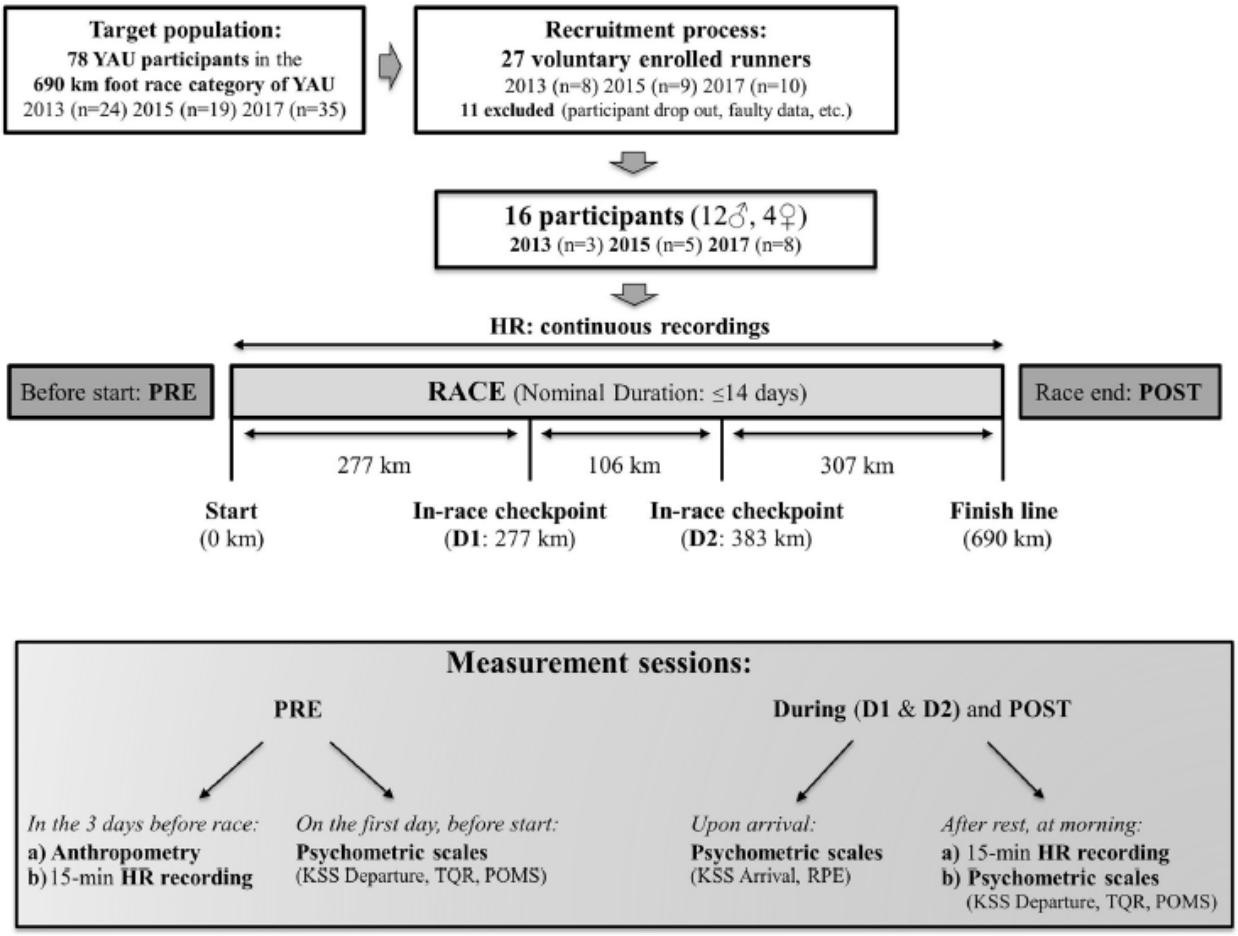

FIGURE 2 | Experimental protocol. Schematic representation of the study protocol and experimental procedure employed in all three YAU races of 2013, 2015, and 2017, except for psychometric assessment (included only in the 2015 and 2017 races).

and complexity (European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Specifically, as for time-domain analysis, the root mean square of the successive RR differences (RMSSD), an indirect index of vagal activity, was calculated. Furthermore, NN50 statistics were computed, specifically, the hourly number of increases (NN50+) or decreases (NN50–) between consecutive NN intervals larger than 50 ms (Ewing et al., 1984), as well as the percentage of such differences with respect to the total number of NN intervals (pNN50+ and pNN50–) (Bigger et al., 1988; Merati et al., 2015). The NN50 statistics may reflect the rate of "vagal bursts," as bursts of vagal outflow are producing NN intervals greater than 50 ms (Ewing et al., 1984). In the frequency domain, the total spectral power density (TP) was assessed together with its components: (i) high frequency (HF) band (0.15–0.40 Hz), which depends mainly on parasympathetic activity and is synchronous with the respiratory sinus arrhythmia; (ii) low frequency (LF) band (0.04–0.15 Hz), which depends on both parasympathetic and sympathetic activity; and (iii) LF/HF ratio, which is currently considered a marker of sympathovagal balance (Ewing et al., 1984). In the non-linear domain, as for complexity analysis, the following indices were assessed: (i) the HR sample entropy (SampEn), which measures the level of irregularity of the NN interval series and mirrors vagal activations or sympathetic deactivations (Porta et al., 2008); (ii) the short-term self-similarity coefficient ($\alpha 1$) and long-term self-similarity coefficient ($\alpha 2$) of NN intervals, as assessed by detrended fluctuation analysis (DFA), mentioned here respectively as DFA$\alpha 1$ and DFA$\alpha 2$ (Peng et al., 1995). Both indices may be affected by parasympathetic tone, whereas, for example, higher DFA$\alpha 1$ is associated with sympathovagal balance increase or vagal tone decrease (Penttilä et al., 2003). The significance of DFA$\alpha 2$ has not yet been completely elucidated, as there is indeed only scarce evidence within the literature. However, it seems to be associated with alertness (Ivanov et al., 1999) and may be influenced by sleep stages, being higher in awake states and REM sleep with respect to light and deep sleep (Schumann et al., 2010).

All HRV indices, except for NN50 statistics (manually calculated), were assessed by means of the Kubios HRV software, ver. 2.1 (Kuopio, Finland), a free available software to assess HRV, widely used in the scientific literature, especially in the field of sport sciences (Tarvainen et al., 2014).

Psychometric Assessment

Karolinska Sleepiness Scale

The Karolinska Sleepiness Scale (KSS) (Kaida et al., 2006), which has been highly validated to sensitively depict objective sleepiness (Kaida et al., 2006; Sallinen et al., 2008), was administered both after rest (before departure in the morning: KSS Departure) and upon arrival (KSS Arrival) (see **Figure 2**). The athletes were asked to rate their subjective sleepiness on a numerical scale ranging from 1 to 10. Specifically, 1–6 are assigned to an "active state" of alertness (1 corresponding to "extremely alert" and 6 to "some signs of sleepiness") and 7–10 to a "sleepy state" (7 corresponding to "sleepy, but no difficulty remaining awake" and 10 to "falling asleep all the time").

Borg Scales

After rest (before in-race departure and at the finish), subjects were administered the Borg Total Quality of Recovery (TQR) questionnaire (Henttä and Hassmén, 1998). The Borg TQR has been demonstrated to sensitively represent the individual recovery status (Freitas et al., 2014), whereas the use of recovery and wellness indicators has exhibited important validity in the monitoring of athletes (Buchheit, 2015; Bisschoff et al., 2016). It consists of a 6–20 numerical scale, with 6 being equivalent to "very, very poor recovery" and 20 to "very, very good recovery," so that the obtained score allows determination of the athlete's subjectively evaluated quality of recovery.

Upon arrival at checkpoints or the finish (**Figure 2**), participants were administered the Borg Rating of Perceived Exertion (RPE) scale (Borg, 1982; Scherr et al., 2013), which is commonly used in athletes to monitor exertion and also the current subjective workload, additionally, in association with cardiac autonomic regulation (Parry et al., 2011; Thorpe et al., 2016; Siegl et al., 2017) and performance (Suzuki et al., 2006). It again consists of a 6–20 numerical scale, 6 being "very, very light" and 20 "very, very hard," the individual score indicating the athlete's degree of subjectively perceived exertion.

Profile of Mood States

At morning, after rest, mood states in the YAU participants were investigated through the Profile of Mood States questionnaire in the short-form (POMS-SF, here referred to as POMS) (Curran et al., 1995). This extensively validated tool is commonly used in athletic monitoring (Hedelin et al., 2000; Leti and Bricout, 2013; Bisschoff et al., 2016) and has been variously observed to be associated with both HRV and performance (Hedelin et al., 2000; Leti and Bricout, 2013; Comotto et al., 2015; Bisschoff et al., 2016). The POMS required participants to state the extent of emotions currently experienced during the last hours (respectively operationalized as "not at all" providing a subscore of 1; up to "extremely," providing a subscore of 5). Analysis of individual subscores in emotional subcategories subsequently provided an individual raw score representing the 6 main mood states Depression, Vigor, Fatigue, Tension, Confusion and Anger, as well as a total sum score of mood disturbance (POMS Total).

The psychometric assessment of mood states in our subjects was further analyzed by comparison with normative data for an athletic sample (Terry and Lane, 2000). This data had been obtained in mixed general athletic samples as well as, amongst others, subgroups of athletes at different competition levels and situations (pre- or post-competition, etc.) (Terry and Lane, 2000). In accordance with Terry, raw scores were transformed to a normalized T-Score (using the individual raw score, group mean and group standard deviation) through the formula: $T\text{-}Score = 50 + [10 + (raw\ score - group\ mean)]/SD$. This transformation converted raw scores to normalized scores on a standard scale with a mean of 50 and a standard deviation of 10, so that individual results could be compared with normative sample data. POMS normative scores of athletes from various sport disciplines, plotted against college student norms originally obtained by McNair in 1971 (McNair et al., 1971), show a distinctive pattern of mood states in athletes compared to sedentary populations, which is referred to as the *Iceberg Profile* (**Figure 9A**). Specifically, athletes have been found to account for significantly higher Vigor, whereas all other (negative) dimension scores remain below mean values for non-athletes, i.e., "under the surface." This distinctive profile has been proposed to indicate greater mental health and reduced mood disturbances in athletic subjects compared to sedentary populations. By plotting individually obtained values against normative data, this specific pattern of higher positive mood and mental health in our participants compared to normative data of sedentary subjects could therefore be assessed.

Moreover, by analyzing result scores of the administered psychometric scales, the so-called *psychological wellbeing* (Scully et al., 1998; Johnston et al., 2015; Saw et al., 2016) was evaluated. A higher psychological wellbeing would correspond to an overall low score both for POMS Total (i.e., higher Vigor, lower Fatigue, Tension, Confusion, Anger and Depression scores) and for fatigue scales (i.e., Borg RPE and KSS), and inversely higher scores for Borg TQR.

Statistics

Data are reported as means ± standard deviations (m ± SD), if not otherwise stated. From 27 enrolled competitors, we included 16 in the statistical analysis (due to early dropouts before D1, as well as related to HRV-data availability and quality). As a result of the extreme conditions of the competition, several participants withdrew before course completion (see section Performance). Therefore, after the race, the entire sample of all participants (ALL) was divided into two subgroups: finishers (FIN: measurements throughout the race until POST) and non-finishers (NON: measurements until D1) (see **Table 1**). Normal distribution was tested with

Shapiro-Wilk and variance with the Equal-Variance-Test. A log-transformation was applied to frequency domain indices to attain normal distribution (Castiglioni et al., 2011). According to the distribution, the variance of HRV parameters, exercise intensity and rest quality and psychometric measurements over the entire race-course in FIN was tested with one-way repeated measures analysis of variance (One-Way RM ANOVA) and *post-hoc* Student's-Newman-Keuls-Test, or Friedman ANOVA on ranks with *post-hoc* assessment through Tukey's Test (i.e., RMSSD, pNN50+, POMS Depression, Borg TQR). In addition, differences in weather conditions between editions were assessed with One-Way RM ANOVA. As all participants reached the first checkpoint, we could implement a direct comparison between the two groups regarding PRE and D1 by applying two-way repeated measures ANOVA (Two-Way RM ANOVA), after normality was passed. Psychometric assessment of mood states was further analyzed through comparison with normative data for athletic samples. In accordance with Terry (Terry and Lane, 2000), raw values of mood states were conversed to standardized T-Scores. Hence, T-Scores could be plotted against the athletic sample mean in order to assess expression of the *Iceberg Profile*, which represents specific mood profiles in athletic subjects. Unpaired Student's *t*-Test was used on raw values, as well as computed T-Scores, to allow comparison of significant differences between YAU participants and normative data for mixed athletic samples. In order to further analyze mood states in YAU competitors, comparison of baseline values (as individual raw scores) with normative data obtained in athletes directly pre-competition, as well as with normative data obtained in athletes post-competition, was performed by application of unpaired Student's *t*-Test. Correlations between HRV indices and psychometric measurements, as well as correlations between HRV indices or psychometric measurements and performance were assessed with Pearson Product-Moment-Correlation or, if normality was not passed, Spearman Correlation. All statistical analyses were performed using SigmaPlot 12.3 (Systat Software, San José, CA, USA). The significance level was set at $p < 0.05$.

RESULTS

Performance

Of the 16 participants included in the statistical analysis (ALL), 10 successfully completed the course (FIN). Due to general fatigue, cardiovascular distress or gastrointestinal problems, as well as injuries (e.g., sprained ankle), 6 withdrew from the competition at earlier points (NON). Baseline anthropometric characteristics of the two subgroups, based on the completion of the race, are presented in **Table 1**. Details of performance are depicted in **Table 2**. The official times recorded among FIN ranged between 225 and 312 h. Specifically, analysis of split times displayed that FIN accounted for 82 ± 15 h (velocity 3.6 ± 0.6 km/h) to reach D1, whereas for NON it took 91 ± 17 h (moving at a velocity of 3.2 ± 0.8 km/h). For FIN, 41 ± 6 h were required to reach D2 (velocity 2.7 ± 0.4 km/h) and 125 ± 21 h to reach the finish line (at a velocity of 2.5 ± 0.4 km/h), so that the overall total finish time (i.e., excluding resting time at checkpoints) was 248 ± 36 h (velocity 2.8 ± 0.3 km/h). A positive correlation between the split times PRE-D1 and D2-POST with respect to the finish time was retrieved (r 0.83, p 0.01 and r 0.93, p 0.001, respectively). This shows that the participants, who were the fastest both in the first and in the last part of the race, also accounted for the best overall time at the end of the race. Such correlations were not found for the split time between D1 and D2.

TABLE 2 | Performance data.

Group	Gender	Distance, km mean (S.D.)	Finish Time, h mean (S.D.)	Velocity, km/h mean (S.D.)
FIN	Men	690.0 (0.0)	254.6 (21.8)	2.7 (0.2)
	Women	690.0 (0.0)	300.2 (18.8)	2.3 (0.2)
	All	690.0 (0.0)	268.3 (29.7)	2.6 (0.3)
NON	Men	384.3 (107.4)	139.3 (60.0)	3.1 (1.2)
	Women	278.4 (0.0)	92.0 (0.0)	3.0 (0.0)
	All	366.7 (105.4)	131.4 (57.0)	3.1 (1.0)
ALL	Men	350.3 (106.4)	206.6 (71.4)	2.9 (0.8)
	Women	358.3 (124.3)	248.1 (105.2)	2.5 (0.4)
	All	352.3 (106.7)	217.0 (79.3)	2.8 (0.7)

Performance data of subgroups (FIN and NON), as well as of all participants (ALL). The overall completed distance and total time to cover it are reported, as well as the overall mean velocity (including resting times). No significant differences between groups.

Heart Rate Continuous Recordings

A total of 185 recordings fulfilled the criteria for analytic inclusion. They were obtained in 15 participants, as one competitor of the 2017 race belatedly volunteered to participate in the study and could not be equipped with the measuring device anymore. As reported above, recorded HR was used as a marker of exercise intensity, by normalizing absolute values with respect to the calculated $\mathrm{HR}_{\mathrm{max}}$. A similar approach was used to define the quality of rest during the actual race, i.e., the time spent at checkpoints was excluded. Results of ExHR (mean HR during exercise as percentage of $\mathrm{HR}_{\mathrm{max}}$) and RestHR (mean HR during rest in between checkpoints, as a percentage of $\mathrm{HR}_{\mathrm{max}}$), classified according to the 4 segments mentioned above, i.e., D1a (36 h after race start), D1b (24 h before arriving at D1), D2a (24 h before reaching D2), D2b (24 h before arrival at the finishing line), are displayed in **Table 3**.

Heart Rate Variability

For all 16 participants, a total of 53 R-R interval recordings were available and exhibited sufficient quality for analysis and assessment of HRV. 16 recordings corresponded to PRE, 13 to D1, and 10 to both D2 and POST. Morning HR pre-, post- and in-race (at checkpoints) is depicted in **Figure 3** and HRV results are depicted in **Figures 4, 5. Figure 4** shows the significant decrease of parasympathetic tone in both groups at D1 compared to PRE, and in the following in-race time-points as for FIN only. **Figure 5** depicts sympathovagal balance indices, where a significant decrease at D1 in both groups of log LF lead to no variations of log LF/HF, whereas in FIN a significant increase of DFAα2 across all time-points was retrieved, and in NON

TABLE 3 | Average exercise intensity and rest quality.

Group	*n*	HR rec. time-point	ExHR, % mean (S.D.)	RestHR, % mean (S.D.)
FIN	9	D1a	70.9 (5.3)	47.4 (8.3)
	8	D1b	62.0 (3.9)*	38.4 (4.4)*
	8	D2a	62.1 (2.6)*	40.0 (3.6)*
	7	D2b	59.1 (4.4)*	37.0 (4.7)*
NON	6	D1a	66.9 (5.6)	44.6 (4.9)
	6	D1b	59.1 (5.8)*	40.0 (3.6)
ALL	14	D1a	69.5 (5.6)	46.4 (7.2)
	14	D1b	60.7 (4.8)	39.1 (4.0)
	10	D2a	60.9 (3.5)	39.6 (3.7)
	8	D2b	57.0 (7.1)	36.2 (4.9)

*Average HR during exercise (ExHR) and at rest (RestHR) across time-points. Data are presented as a percentage of the maximal HR (HRmax) for mean HR during exercise (ExHR) and mean HR during rest periods (RestHR). D1a: HR recorded in the first 36 h; D1b: HR recorded during the 24 h before arriving at D1; D2a: HR recorded during the 24 h before arriving at D2; D2b: HR recorded during the last 24 h before reaching the finish line. Data for the whole sample (ALL) are also reported. *$p < 0.05$ vs. PRE within subgroup (One-Way RM ANOVA).*

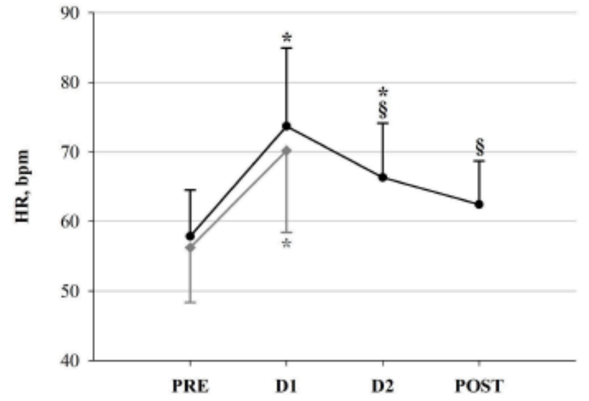

FIGURE 3 | Heart Rate (HR) in FIN (black line) and in NON (gray line) across time-points. *$p < 0.05$ vs. PRE within subgroup (One-Way RM ANOVA). $^{\S}p < 0.05$ vs. D1 (One-Way RM ANOVA).

only a significant increase at D1 as for DFAα1. Between PRE and D1, an overall decrease in TP could be observed in both groups (FIN: $-1{,}964.7$ ms^2 and NON: $-3{,}699.6$ ms^2), but the decrease was only significant (p 0.02) in NON. In fact, in NON the decrease in parasympathetic drive was to some extent greater when compared to FIN, as indicated by DFAα1, which was significantly higher at D1 only in NON (**Figure 5**), and by the difference between PRE and D1 in values of RMSSD: -34.1 ms in NON (p 0.01) and -18.1 ms in FIN (ns) and log HF: -0.8 ms^2 (p 0.04) in NON and -0.5 ms^2 (ns) in FIN.

Only in FIN, a significant negative correlation between HR and mean running velocity, as well as between HR and pNN50+, was detected at PRE (**Figure 6**). The negative correlation between HR and vagal tone indices was observed also at D1, as for pNN50- (r -0.82 p 0.02), and NN50- (r -0.82, p 0.02) with respect to HR. This could not be detected in NON.

Psychometric Scales

Psychometric measurements were performed in competitors of the 2015 and 2017 races, so that a total of 45 assessments (13 in PRE, 13 in D1, 10 in D2 and 9 in POST) were included in the statistical analysis. Results of the POMS questionnaire revealed significant decreases in POMS Vigor and Tension, associated with an increase in Fatigue and POMS Total scores (**Figure 7**). No changes in POMS Depression, Confusion and Anger scores were observed, nor significant differences between FIN and NON at D1. As for fatigue scales, i.e., Borg RPE, Borg TQR and KSS, results are depicted in **Figure 8**. In NON, values of KSS Departure scores were significantly higher at D1 than at PRE. However, as for the other psychometric scores, no significant between-group differences could be detected.

Nevertheless, at PRE, positive correlations between several indices of vagal tone (RMSSD: r 0.86, p 0.03; NN50+: r 0.90, p 0.01; NN50–: r 0.89, p 0.02; pNN50+: r 0.87, p 0.03; pNN50–: r 0.87, p 0.03; log HF: r 0.87, p 0.03) and Borg TQR were detected in NON only, so the higher the vagal tone, the higher the TQR score. Moreover, at PRE, again in NON only, a negative correlation between POMS Fatigue and pNN50+ (r -0.82, p 0.04) was observed, which indicates that the lower the vagal tone, the higher POMS Fatigue. On the other hand, in FIN at D1, a negative correlation was observed between HR and KSS Departure (r -0.85, p 0.02), indicating that the lower the HR, the higher the KSS Departure score; this was associated with a positive correlation between both pNN50– (r 0.84, p 0.02) and NN50– (r 0.84, p 0.02) and KSS Departure, which confirmed that a lower HR and a higher vagal drive were coupled with higher sleepiness; additionally in FIN at D1, there was a positive correlation between Borg TQR and DFAα2 (r 0.81, p 0.03): the higher the TQR score, so the quality of recovery after rest, the higher the DFAα2.

POMS T-Scores of YAU participants were plotted against normative data to provide the above-mentioned *Iceberg Profile* (Terry and Lane, 2000), which depicts POMS Vigor to be significantly higher and all other (negative) dimension scores to be significantly lower compared to mean values for a sedentary population. Analysis of variance between YAU participants and normative athletic data revealed distinctive differences, which are depicted in detail in **Figure 9B**. In comparison to the athletic sample, raw and T-Scores at baseline were significantly lower in ALL regarding POMS Depression, Anger, Fatigue and Confusion, but also Vigor. This was similarly observed when plotting YAU scores against normative data for athletes before and after competition. Compared to pre-competition normative data, YAU subjects at PRE displayed significantly lower Depression, Anger, Confusion and Fatigue, whereas Tension and Vigor were not different (**Figure 9C**). At POST, there were no significant differences between normative data for athletes in post-competition situations and the YAU subjects, except for significantly lower Vigor in YAU (**Figure 9D**).

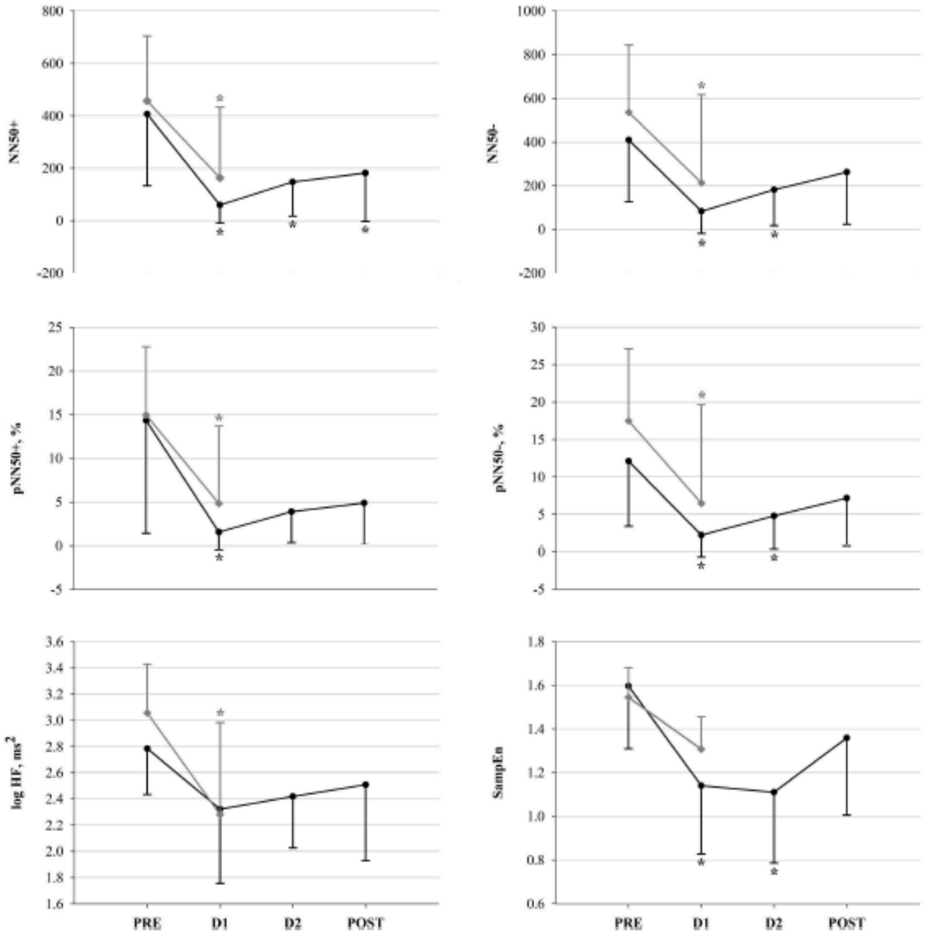

FIGURE 4 | Vagal modulation indices in FIN (black line) and in NON (gray line) across time-points. $^*p < 0.05$ vs. PRE within subgroup (all variables: One-Way RM ANOVA; pNN50+: Friedman ANOVA).

DISCUSSION

To our knowledge, this is the first study investigating cardiac autonomic modulation and psychological correlates during ultramarathon in a subarctic environment. This setting provided the unique combination of three extreme environments: (i) ultra-endurance exercise performance (Perini and Veicsteinas, 2003; Scott et al., 2009), (ii) arduous environmental circumstances (Maughan et al., 2007), such as severe continuous cold exposition, and (iii) sleep deprivation/disturbances, induced by the condition of outdoor living during the race (Stein and Pu, 2012). The interplay of each single component of this *three-folded stress stimulus*, amplifies and affects several physiological and psychological aspects, which may be reflected in physical performance outcomes. Regarding race results, 10 of 16 subjects successfully completed the 690 km ultramarathon. Taking into account characteristics and conditions of the competition (see section The Yukon Arctic Ultra: The Longest, the Coldest Ultramarathon), the distribution of measurements sessions (see section Experimental Protocol and Measurements and **Figure 2**) holds great importance to interpret observations. In fact, the greatest effect on autonomic cardiac modulation, mood and fatigue was observed in the race segment between PRE and D1 (i.e., more than one third of the entire race); this may have been related to: (i) the initial stress of entering the race (i.e., performance demands coupled with environmental conditions), (ii) the different characteristics of the three parts of the race (see section Experimental Protocol and Measurements), and (iii) the running strategy of successful participants. Indeed, by analyzing the split times between measurement sessions, a positive correlation between the first and the final split time was found. This indicates that the fastest competitors in PRE-D1 (and D2-POST), were also the fastest finishers. The challenge of this first part of the race would be significantly underlined by this observation, and it provided ulterior evidence of the central role of the ability to cope with in-race demands at

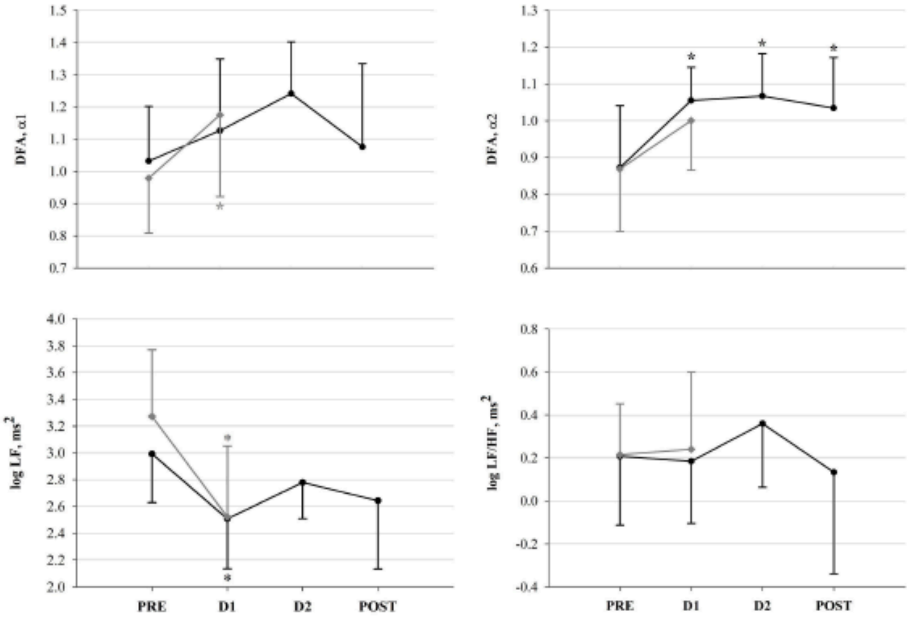

FIGURE 5 | Sympathovagal balance indices in FIN (black line) and in NON (gray line) across time-points. $^*p < 0.05$ vs. PRE within subgroup (One-Way RM ANOVA).

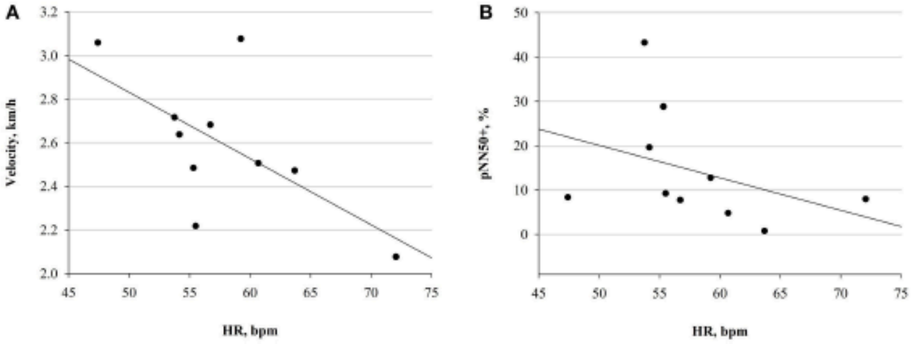

FIGURE 6 | Correlations at PRE in FIN group. **(A)** Correlation between HR and mean velocity ($r = -0.63$; $p = 0.04$). **(B)** Correlation between HR and pNN50+ ($r = -0.67$; $p = 0.03$).

very early time-points (i.e., directly after entering the race) for optimal adaptation. Therefore, during the first kilometers, successful competitors could already be recognized. This is in line with previous investigations on early recognition of successful competitors by their initial pacing strategies (Renfree et al., 2016; Bossi et al., 2017). Specifically, Lambert et al. observed more successful competitors in a 100 km ultramarathon to display higher velocities than lower performing athletes in the early race stages (Lambert et al., 2004). Moreover, the continuous significant decrease in ExHR in FIN, associated to a concomitant decrease of RestHR ($p < 0.05$ across all time-points vs. PRE), reflected decrements in performance, while the need of rest increased. On the other hand, the continuous decrease in RestHR may also indicate higher quality of recovery (Waldeck and Lambert, 2003; Silvani and Dampney, 2013), demonstrating that successful competitors had higher recovery potential, as they attained a higher quality of rest. Indeed, by comparing FIN and NON, we found a significant decrease of RestHR between PRE and D1 in FIN only.

In line with Millet (Millet and Millet, 2012), our observations show that ultramarathon might be an excellent model to test the adaptive potential under extreme conditions. However, in our case, we have to take into account not only potential effects of ultraendurance exercise, but the interplay of three factors (i.e., *three-folded stress stimulus*) on influencing

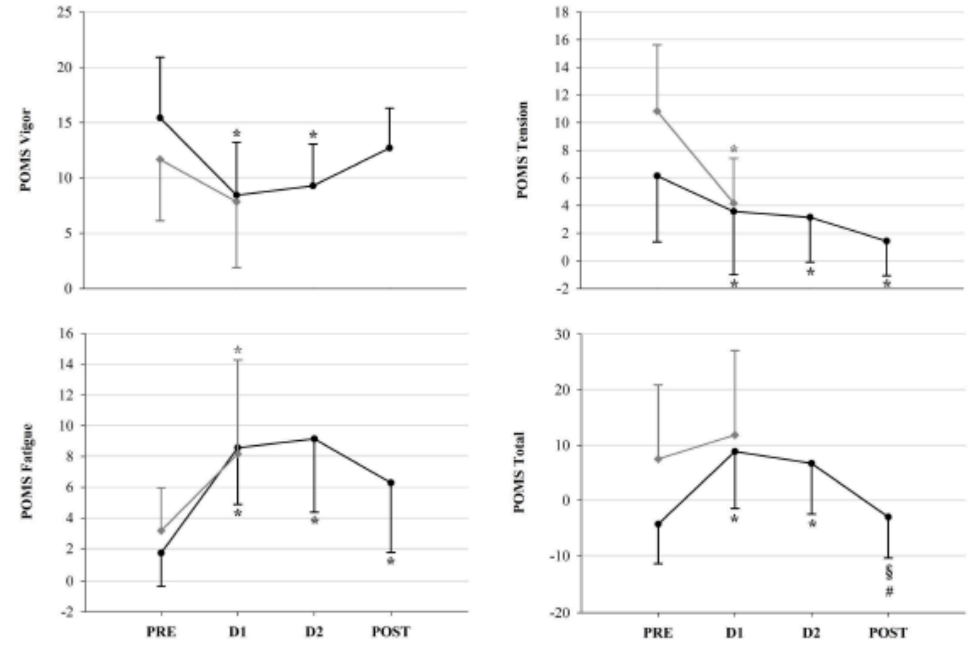

FIGURE 7 | POMS mood state scores in FIN (black line) and in NON (gray line) across time-points: $^{*}p < 0.05$ vs. PRE within subgroup; $^{\S}p < 0.05$ vs. D1; $\#p < 0.05$ vs. D2 (One-Way RM ANOVA).

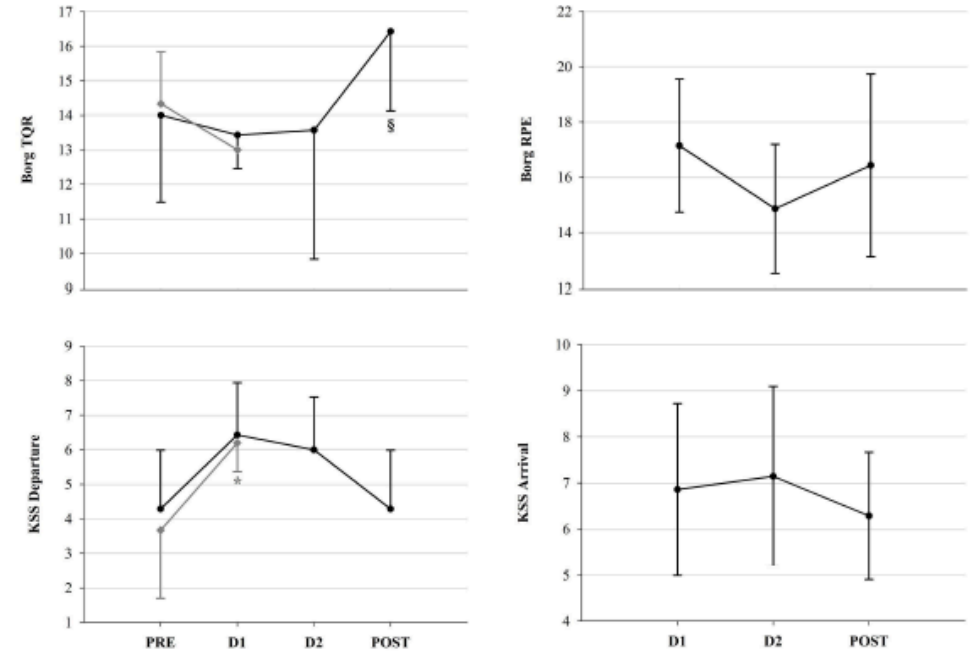

FIGURE 8 | Fatigue scale scores. Borg and KSS scores in FIN (black line) and in NON (gray line) across time-points. $^{*}p < 0.05$ vs. PRE within subgroup; $\S p < 0.05$ vs. D1 (One-Way RM ANOVA).

autonomic cardiac modulation and psychometric aspects: strenuous exercise, living outdoors in subarctic winter and sleep deprivation/disturbances.

Autonomic Cardiac Control and Endurance

An overall reduction of vagal drive, as well as total HRV, has been widely observed during acute exercise and competition (Perini

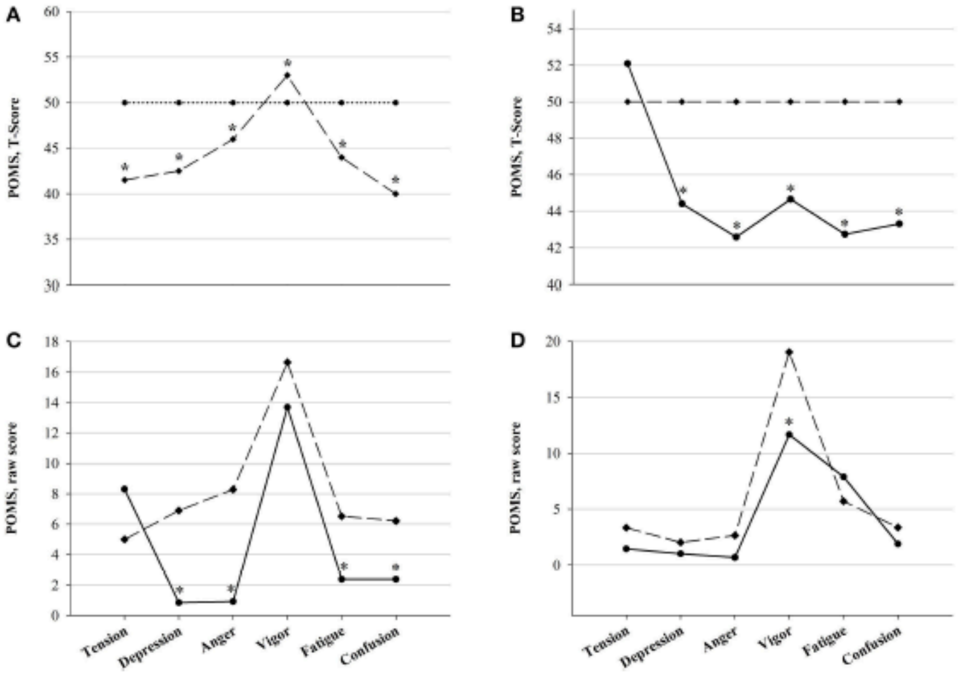

FIGURE 9 | Comparison of POMS results with normative data (Unpaired Student's *t*-Test). **(A)** *Iceberg profile* of mood states in an athletic sample (dashed line) plotted against sedentary subject norms (dotted line), **(B)** Mood states in all YAU subjects (ALL, solid line) plotted against normative data for mixed athletic samples (dashed line), **(C)** Mood states in ALL at PRE (solid line) plotted against normative data for pre-competition assessment (dashed line), **(D)** Mood states in ALL at POST (solid line) plotted against normative data for post-competition assessment (dashed line): $^*p < 0.05$ between groups.

and Veicsteinas, 2003; Buchheit et al., 2010). After cessation of exercise, parasympathetic predominance is gradually restored, depending on the preceding intensity, the training status and the quality of recovery, as reported also in previous studies on ultramarathon (Gratze et al., 2005; Scott et al., 2009; Foulds et al., 2014), and this is in line with our results. However, due to the very long distance of YAU we did observe already a vagal tone recovery before the end of the race, in successful participants (**Figure 4**). Considering that our HR recordings were collected after several hours of rest, early at morning during the race, the significant increase in HR (**Figure 3**) clearly describes the inability for participants to recover completely, as HR remained significantly higher at both D1 and D2. Nevertheless, at D2, HR decreased again with respect to D1 (−7.8 bpm, *p* 0.03), remaining, however, significantly above baseline values. At POST, HR was significantly lower than at D1 (−11.3 bpm, *p* 0.004) and not different from PRE. This would demonstrate that successful competitors (i.e., FIN) were able to positively adapt by recovering toward baseline conditions. This specific trend of HR can also be compared with observations in functional overreaching training interventions, where, initially, the increased training stimulus promotes a decrease in vagal drive (i.e., increase in HR), but, due to optimal adaptation, this is subsequently recovered (Buchheit, 2015; Bellenger et al., 2017). Indeed, in our participants, the increased HR between PRE and D1 was modulated via a significant attenuation in vagal tone in both groups (**Figure 4**). This, associated with a significant concomitant decrease of log LF, lead to an overall reduced HRV (see result section for TP). Additionally, evidence of reduced parasympathetic drive at D1 was further underlined by significant decreases in SampEn in FIN (**Figure 4**). In line with previously investigated implications of reduced SampEn values, this suggest lower responsiveness to environmental stimuli under attenuated entropy (Sassi et al., 2015). Interestingly, our findings indicate that in unsuccessful participants (i.e., NON), this parasympathetic drive decrease was to some extent greater than in FIN. This was shown firstly by the significantly higher DFAα1 at D1 in NON only (**Figure 5**), which has been associated to vagal tone decrease (Penttilä et al., 2003), and secondly by the difference in values of RMSSD and log HF for NON vs. FIN between PRE and D1 (see results section). Taking into account that in athletic subjects, stress has been associated to lower HRV and depressed parasympathetic drive (Nuissier et al., 2007; Cervantes Blásquez et al., 2009), this suggests that successful participants were able to efficiently relax and therefore fall asleep. The stronger decrease of vagal tone in NON, indeed, may indicate that these participants, ultimately unable to complete the race, were characterized by an impaired ability to cope with the in-race demands, already at early points of the competition, which may be reflected by lower quality of recovery (i.e., sleep quality impairment), whereas FIN displayed higher recovery potential. In turn, this supports the hypothesis that in such extreme conditions, vagal tone modulations may mirror the individual's ability to adapt, showing in resilient individuals earlier and efficient increase of parasympathetic tone, after the large initial decrement. Between PRE and D1, we also observed the typical reduction of overall HRV, which normally occurs during exercise, as well as a significant reduction of log LF in both groups, thus leading to non-significant changes in log LF/HF ratio (**Figure 5**). Only in FIN, DFAα2 was significantly higher at D1 compared to baseline and remained higher at both D2 and POST. As the exact implications of this non-linear HRV index have not been elucidated, this is an interesting finding. Previous investigations have reported that DFAα2 would decrease after the application of clonidine, an imidazoline-derived centrally-acting α2-adrenergic agonist and hypothalamic inductor of hypotension, which affects the overall sympathetic activity by resetting it to a lower setpoint (Castiglioni et al., 2011). Conversely, increased DFAα2 values have been reported in subjects who were awake compared to when asleep, but have also been linked to sleep stages, being higher in awake states and REM sleep than during light and deep sleep (Schumann et al., 2010). These findings allow us to hypothesize a link between increased DFAα2 and hyperarousal or enhanced alertness and vigilance, which in this case would be driven by the sympathetic branch of the vegetative nervous system. As we reported a significant increase in DFAα2 during the race, which persisted up until POST, this interpretation concurs very well with our observations (**Figure 5**). Higher values of DFAα2 could have been induced by an increased need for vigilance (i.e., sleeping outdoors during the subarctic winter in the Yukon Territory), leading to sleep impairment and/or deprivation, and to a general acute stress response promoting hyperarousal. Furthermore, the negative correlation between HR and velocity, paired with the negative correlation between pNN50+ and HR at PRE only in FIN (**Figure 6**), indicated that a lower HR in association with a higher vagal tone would predict a better performance. In FIN, the persistency of the above-mentioned negative correlation of vagal indices with HR at D1 (see Results section), demonstrated how, in our study, the observed increase in HR was specifically driven by a decrease of parasympathetic tone. This mechanism was mirrored mainly by time domain indices of vagal drive, i.e., NN50 and pNN50 statistics, which are linked to mean HR. Indeed, while pNN50+ quantifies the rate of HR decelerations (increase in successive R–R intervals), NN50– quantifies the rate of HR accelerations (decrease in successive R–R intervals) (Merati et al., 2015). At PRE, our data showed a negative correlation between HR and pNN50+ (i.e., rate of successive HR decelerations) and at D1, HR correlated negatively with both pNN50– and NN50– (i.e., rate of successive HR accelerations). Differences in the distribution of HR decelerations and accelerations have been associated with the enhanced presence of sympathetic modulations, whereas the HR decelerations have been identified as a better marker of vagal activity (Merati et al., 2015). This further demonstrates that at the beginning of the race, between PRE and D1, the reduction of vagal tone determined the increase in HR. Indeed, at D2 and POST, no correlation between vagal indices and HR could be detected. During this second in-between measurement section, HR decreased with respect to D1. Concomitantly, a slight increase of vagal tone was observed (**Figures 3, 4**). After D1, the correlation between HR and vagal tone disappeared, indicating that the increase of parasympathetic tone was not able to elicit *per se* the decrease in HR. Instead, it would be suggested that the observed HR reduction also occurred due to other concurrent factors as for example psychological states. In fact, at D2, a significant reduction of POMS Total scores (indicating increased negative mood states or disturbance) with respect to D1 was found (**Figure 7**). This was associated with a decrease of Borg RPE at D2 (although not significant), suggesting that psychological factors were involved in recovering overall wellbeing, and thus were associated with reducing the HR (see section Psychological Wellbeing).

Psychological Wellbeing

We observed an overall decrease of psychological wellbeing across the whole ultramarathon (**Figures 7, 8**). Interestingly, the POMS Tension item exhibited significantly higher values already at PRE with respect to D1 in both groups, in particular in NON (+6.7 vs. +2.6 in NON vs. FIN). This may reflect pre-competition anxiety. In fact, during the subsequent race, POMS Tension decreased significantly across all time-points. The concurrent increase in Vigor from D2 onwards (as POST values were no longer significantly lower in respect to PRE), may be related to the recovering process of positive mood, but also to the fact that participants were succeeding in the race and the finishing line was getting closer. Between PRE and D1, a significant reduction of positive mood items (lower POMS Vigor and higher Fatigue as well as POMS Total scores) had been observed. Therefore, we can infer that psychometric measurements sensitively reflected the impact of this extremely demanding competition on different subgroups, more strongly affecting those subjects that were unable to cope with the in-race demands. Nevertheless, after D1, it was possible to recognize a particular pattern in FIN, who recovered their wellbeing and positive mood. Indeed, not only POMS Tension scores continuously decreased, but also Vigor again attained values comparable to baseline at POST. Enhanced positive mood or motivation may have furthermore contributed to the observed recovery of vagal tone. In fact, previous investigations have demonstrated associations between enhanced parasympathetic drive in the frequency domain and POMS Vigor, as well as energy index (i.e., the POMS Vigor/Fatigue ratio) (Bisschoff et al., 2016), and the Vigor subscale has been proposed as a marker of the overall autonomic nervous system modulatory activity (Nuissier et al., 2007).

As mentioned above, this finding could be related to the fact that completion of the race was approaching. On the other hand, we found significantly lower POMS Total scores (indicating reduced mood disturbance) paired with higher Borg TQR values at D2 compared to D1 (even if not reaching statistical significance). This reflects a trend of increase in psychological wellbeing. As at POST, POMS Total was similar to PRE values, but significantly higher than at D1 and D2, successful recovery of mood disturbance in FIN is accentuated.

Moreover, during the first part of the race, as mentioned above, the increased HR depicted the inability of participants to recover completely. However, this event was not reported by data of the Borg RPE scale (**Figure 8**), which, although in-race values had decreased, did not exhibit any significant changes across the race. In this sense, it is likely that in the case of the YAU competitors, the Borg RPE failed to detect the perceived exertion.

Results of Borg TQR in NON showed a significant correlation between vagal indices and TQR scores at PRE, which may suggest that the higher the parasympathetic tone, the higher the perceived quality of recovery, underlining previous findings about the effect of parasympathetic tone on perceived fatigue in athletes (Bisschoff et al., 2016). However, this correlation was not found at D1. Instead, only in NON, KSS Departure scores were higher at PRE compared to D1. As the KSS has been extensively validated to depict objective sleepiness (Kaida et al., 2006), this subjective measurement indicates greater sleepiness, probably due to impaired rest and insufficient recovery in NON compared to FIN.

At PRE, no correlation between psychometric scales and HRV indices was found in FIN. Nonetheless, at D1, KSS Departure correlated negatively with the HR and positively with vagal indices in FIN, i.e., the lower the HR and the higher the vagal tone, the higher the subjective sleepiness upon departure. On the other hand, the concomitant positive correlation between Borg TQR and DFAα2 could suggest that subjects with higher recovery and better sleep quality, were also in a state of enhanced vigilance and alertness, ready to continue on the trail. Nevertheless, we must admit that as we recorded HR early in the morning, just after awakening, and DFAα2 has been reported to be higher in awake states and REM sleep than in light and deep sleep (Schumann et al., 2010), our observations could also be influenced by the circumstances of the measurement sessions, immediately after waking up. The high adaptive potential in our FIN subjects promoting recovery of initially increased mood disturbance, exertion and sleepiness, paired with a concurrently re-increasing subjective recovery status, presents several implications. Possibly, lower sleepiness and therefore higher alertness would yield essential importance for coping with the environmental challenges of the YAU competition. Moreover, sleepiness and fatigue have been associated with impaired cognitive, as well as physical, function and performance (Fullagar et al., 2015). Therefore, the ability to recover from attenuated psychometric wellbeing in our high-achieving FIN once more underlines the importance of adaptability.

Finally, comparison of mood states with normative data for athletic samples (Terry and Lane, 2000) generally displayed lower mood disturbance in our competitors (**Figure 9**). At baseline, POMS Depression, Fatigue, Confusion and Anger were lower, with Vigor conversely being higher compared to normative scores. Further comparison with normative data for pre- and post-competitive assessment again confirmed the great mental health in our participants, who had significantly higher positive mood than compared to pre-competitive normative values. During the first stages of the race, mood disturbance significantly increased under the exhausting demands, but recovered. Therefore, at POST, mood states in YAU participants (except for Vigor scores) did not significantly differ from normative data in post-competition assessment. To conclude, the high adaptive capacity in our subjects, who attained recuperation of gravely impacted mood states after enduring the extreme in-race conditions and stress stimuli, is again underlined.

Practical applications of these findings are related to training methods, highlighting the importance of high and/or fast increasing vagal tone, and of mood states: the "mind," i.e., mood state and motivation, plays a crucial role, especially with respect to such a long-lasting and highly demanding competition. In fact, successful competitors were able to perform greatly also in the second part of the race, where the decrease of HR was not coupled directly with higher vagal drive (as instead was in the first part of the race for FIN only), and the intervention of psychological aspects could be hypothesized (see above). All in all, assessment of HRV and psychological profile may contribute to monitor and partly predict performance in such extreme environments.

LIMITATIONS

Given that this is an in-field study in extreme environments, a number of possible limitations must be addressed.

First of all, the sample size of 16 may appear small, however, considering that a total number of only 78 athletes competed in the three investigated editions and 27 of them enrolled in our study, we regard this number to be quite considerable and sufficient under these specific conditions.

Moreover, there is a substantial difference in the distance between the in-race checkpoints (i.e., D1, D2) selected to perform measurement sessions and a study protocol over three equispaced checkpoints may have been favorable. However, the choice of measurement implementation was due to essential practical concerns, as previously mentioned (see section Experimental Protocol and Measurements). These concerns also held essential importance for standardizing as much as possible measurement conditions, (i.e., indoors facility, comfortable setting regarding space, temperature, noise, and light exposure), especially regarding HR beat-to-beat recordings.

Furthermore, we aimed to allow comparison of additional data from HR continuous measurements with HRV and psychometric parameters obtained at measurement points. Therefore, continuous HR recording data were clustered and were split up in the above-mentioned four sections (see section Performance Assessment and Heart Rate Continuous Recordings).

CONCLUSION

The main findings of this study are: (i) the extent of the early vagal withdrawal, associated to the timing and potential of its recovery, is crucial for success in this specific competition, (ii) a pre-competition lower resting HR, coupled with a higher vagal tone, would predict a better performance, as already reported in the literature for endurance sports (Gratze et al., 2005; Buchheit, 2014), and (iii) psychological profile and wellbeing is reliably depicted by mood state assessment with the POMS questionnaire, but not by Borg fatigue scales, and again associated with autonomic cardiac modulation. Successful ultramarathoners were coping better already in early stages of the competition, which allowed recovery of cardiac autonomic balance and positive mood, thus associated with higher athletic achievement. Therefore, assessment of HRV and psychological profile may contribute to monitor and partly predict performance in such extreme long-duration competitions in extremely cold environments.

AUTHOR CONTRIBUTIONS

LR and MM contributed equally to the study by writing the manuscript and analyzing the data. MS designed, planned and implemented the study, secured funding sources, and performed measurements and data collection. AS assisted with the measurements and data collection. AR-R, LR, and MM performed statistical analyses. RC and H-CG contributed to the study design, provided expertise and feedback. LR formatted, and, with assistance of MM and MS, revised the manuscript.

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2.5 Fifth paper. The *stressed heart*: exercise in physical and mental stress

Prell R, Opatz O, Merati G, Gesche B, Gunga HC, **Maggioni MA.** (2020) *Heart Rate Variability, Risk-Taking Behavior and Resilience in Firefighters During a Simulated Extinguish-Fire Task*. Front. Physiol. 11, 482

In this article, not only heart response to exercise in extreme conditions, but also specific personality traits are investigated in a very particular population: fire-fighter officers from the Berlin Brigade. During their professional activity, fire-fighters face very often emergency and high-risk situations. Thus, they must be physically able to perform their tasks but at the same time, must be able to keep constantly alertness, clarity of mind, emotional control, and get an accurate general view of the situation, to quickly decide the most suitable intervention, according to the sudden unexpected situation that they may face. Aims of this study are: 1) to evaluate acute effects on the heart of physical exercise performed in extreme hot and dangerous conditions; 2) to analyze cardiac autonomic modulation; 3) to explore the correlation between HRV indices and personality traits, as resilience and risk-taking behavior, which are key factors for professional fire-fighters.

A group of twenty male officers was selected. Data collection was performed during a typical training session, which consisted in a fire-extinguish task inside a container set on fire, including, for half of the sample (Ex) repetitive bouts of resistance exercise (rowing), while being inside the container. The other half of participants (NoEx) was resting, as well in sitting position. HR recordings with a heart rate monitor (duration: 20 min) were performed i) at morning, on the testing day, upon awakening, at home, lying (baseline); ii) before entering the container, in a separate room, close to the training place, sitting (pre); iii) during, inside the container, Ex vs NoEx, sitting (during), and iv) after, in the same place as before, sitting (post). Validated scales for resilience, risk-taking behavior and individual stress load (i.e., Risk-taking Scale (R-1), Resilience Scale (RS-13) and the NASA-Task Load (NASA-TXL)) were administered after (post) deployment in the container only.

As expected during fire-extinguish task the Ex group showed significantly higher HR values with respect to NoEx group, which persisted also during early recovery. Despite the exposition of both groups to very high temperature (up to 150 °C) and the same body posture, short-duration, repetitive bouts of resistance exercise induced an additional strain, which could be matched by the cardiovascular system with a further increase of HR. Risk-taking behavior correlated with morning depressed vagal tone, whereas resilience was correlated to baseline higher vagal tone.

HRV analysis appears a promising tool to bridge the gap between physiology and psychology among this specific population and could be helpful as a marker in the selection procedure for future fire-fighters, as well as a periodical health monitoring tool for professional active officers.

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Heart Rate Variability, Risk-Taking Behavior and Resilience in Firefighters During a Simulated Extinguish-Fire Task

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Firefighters face a high-risk potential, thus their psychological ability to cope with critical or traumatic events is a crucial characteristic. This study examines correlations between cardiac autonomic modulation, risk-taking behavior, and resilience in professional firefighters. Twenty male professional firefighters underwent a 20 min beat-to-beat heart rate (HR) monitoring at baseline in the morning upon awakening, then before, during and after a realistic deployment in a container, systematically set on fire. Risk-taking behavior, resilience, and subjective stress were assessed by specific validated tools after deployment: the *Risk-taking Scale* (R-1), the *Resilience Scale* (RS-13), and the multi-dimensional *NASA-Task Load Index*. The cardiac autonomic modulation at rest and in response to stress was assessed by classic indexes of heart rate variability (HRV) as RMSSD and LF/HF ratio. Results showed that: (i) risk-taking behavior correlated with a withdrawal in vagal indices, shifted the baseline sympathovagal balance toward sympathetic predominance (LF/HF ratio $r(8) = 0.522$, $p = 0.01$), and increased mean HR both in baseline and during physical exercise ($r(8) = 0.526$, $p = 0.01$ and $r(8) = 0.445$, $p = 0.05$, respectively); (ii) resilience was associated with higher vagal indices (RMSSD $r(18) = 0.288$, $p = 0.04$), and with a baseline sympathovagal balance shifted toward parasympathetic predominance (LF/HF ratio $r(18) = -0.289$, $p = 0.04$). Associations of risk-taking behavior and resilience with cardiac autonomic modulation could be demonstrated, showing that HRV may be a valuable monitoring tool in this specific population; however further studies are warranted for validation.

Keywords: autonomic nervous system, autonomic modulation, heart rate variability, risk-taking behavior, resilience, cardiac stress, workload, firefighters

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INTRODUCTION

Saving lives under adverse environmental conditions with consciously endangering one's own well-being, is a constant challenge for the fire service. The working environments of firefighters are characterized by extremely demanding conditions, such as disaster missions, rescue services with an uncertain outcome, as well as firefighting in extremely hot and hostile environments. The working hours are irregular and obligations, such as the recovery of injured or dead people, encumber the mental and physical constitution. Hardly any other job requires a corresponding physical condition and a stable mental state.

Studies mentioned that the typical workload of the task forces correlates with an increased risk of chronic lung diseases (Guidotti, 1995; Weiden et al., 2010; Weakley et al., 2016), cardiovascular diseases (Vrijkotte et al., 2000; Koh et al., 2005; Al-Zaiti and Carey, 2015; Hunter and Mills, 2017), and cancer (LeMasters et al., 2006; Burgess et al., 2018), but also results in mental diseases, such as Post-Traumatic Stress Disorder (Haslam and Mallon, 2003; Blackburn and Owens, 2016; Flatten et al., 2016; Quan et al., 2017; Lee, 2019).

The willingness of firefighters to expose themselves to potentially deadly situations cannot be viewed separated from its psychological dimension. In the past, bravado behavior was postulated, which led to the public perception of a masculine and heroic image of the firefighters (Ericson, 2014). Risk-taking behavior determines the situational awareness, decision-making and the selection of actions—patterns of behavior that affect the interaction and team performance (O'Neill and Rothbard, 2017). Therefore, and because risk-taking behavior also leads to an increased sense of invulnerability (Greene et al., 2000), critical situations can arise. Nevertheless, this circumstance has received relatively little attention so far.

It becomes clear that firefighters face a high-risk potential, which has to be minimized by appropriate training programs. These programs often involve a realistic deployment simulation in a container which is systematically set on fire and has to be deleted from the inside out. Such exercises are tactically adapted to real deployments and provide the unique possibility to observe human behavior and physical adaptations in controlled surroundings.

A further feature to be considered is resilience, defined as the ability to cope with crises in the life cycle by using personal and socially mediated resources and to use them as an opportunity for development (Welter-Enderlin, 2006; Southwick and Charney, 2018). In this sense, resilience has to be understood as a multidimensional, dynamic, and compensatory process that varies over the life span and is strongly depending on the situational and individual state. For employees of fire departments, who face potentially traumatic situations every day, resilience is a profound mental advantage for work ability and quality of life.

Unfortunately, personality traits such as risk-taking behavior and personality states such as resilience are traditionally assessed by self-reports and questionnaires, methods that are prone to reporting biases. A solution to this problem is the introduction of standardized and validated physiological and biological predictors (biomarkers) that allow an objective assessment of both physical and mental processes. The heart rate variability (HRV) is considered a reliable instrument for detecting modulation of heart rate (HR) by the autonomic nervous system (see Task Force of the European Society of Cardiology, 1996; Salters-Pedneault et al., 2010; Minassian et al., 2014), and in the broadest sense a tool to measure stress and stress responses to different stimuli. This tool has successfully been used in to evaluate the human social behavior (Schmidt and Fox, 1994; Tang and Schmidt, 2017). Such measurements are easy to perform and completely non-invasive, and therefore find application in many fields.

The primary aim of this work was to assess whether HRV can be used as a reliable marker for risk-taking behavior and resilience in a group of professional firefighters. The secondary aim was to evaluate the conditions of measurement of this parameter that best predict the psychological attitude to face dangerous situations for these workers (at rest, pre-, during, and post-exposure to simulated stressful conditions of typical working risk and under varying physical workload). Finally, we aimed at observing whether the (possible) additional effect of physical workload during psychological stress might influence HRV.

MATERIALS AND METHODS

Subjects

The sample included $n = 20$ male firefighters in active fire service. All participants were members of the professional fire brigade of Berlin. The average age of the sampled firefighters was 37.8 ± 10.9 (m ± SD) years, ranging from 20 to 59 years. Socio-demographic and work-related data were collected for all participants (see **Table 1**).

Psychometric Questionnaires Administration

To collect the psychometric data, three questionnaires were used. The risk-taking scale (R-1) by Beierlein et al. (2014) measures the general willingness to take risks with only one item, in the format of a seven-level rating scale with the poles (1) "not at risk" to (7) "very willing to take risks." The test results are evaluated according to age, since risk-taking behavior is subject to minor changes during lifetime (Josef et al., 2016). Average values of 4.62 ± 1.39 on the 7-points scale (where the maximum is 7) were found in the standardization for male participants aged 18-35 years reported by Beierlein et al. (2014). Participants aged 36–65 years reached values of 3.76 ± 1.56 and the group of 65 years and above values of 3.51 ± 1.63 (Beierlein et al., 2014). If a person reaches higher values than the age-specific reference, that person can be expected to be more willing to take risks.

For the assessment of resilience, the Resilience Scale (RS) of Wagnild and Young (1993) was selected. The objective of the RS is to capture the internal personal resources and their contribution to the positive resolution of critical life events. The short version with 13 items (RS-13) by Schumacher et al. (2005) allows to recognize persons who are more heavily burdened than other. Similar to the R-1, the answer format is presented on a

TABLE 1 | Socio-demographic characteristics of the sample.

		***N* = 20**
		n
Service experience in years	5	4
	6–10	11
	11–20	0
	>20	5
Weekly sports in hours	None	1
	1 h	5
	<1–3 h	6
	More than 3 h	8
Smoking	Never	5
	Quit smoking more than a year ago	7
	Quit smoking less than a year ago	2
	Yes	6
Alcohol consumption per month	Never	1
	Rare (1–4x/month)	8
	Sometimes (5–10x/month)	6
	Frequently (every third day)	5
Drug therapy	None	20

seven-level rating scale, comprising statements ranging from (1) "completely agree" to (7) "do not agree," so the highest possible score is 91. According to information of standard values by Schumacher et al. (2005) ranks are determined. A score between 13 and 66 can be considered as a low expression of resilience. A score between 67 and 72 can be considered as moderate expression and a score between 73 and 91 as a high expression of resilience. According to Schumacher et al. (2005) the average for resilience is around 70 ± 12 points.

In order to assess the subjective stress during fire contact the multi-dimensional NASA-Task Load Index (NASA-TLX) by Hart and Staveland (1988) was selected, since it has proven to be sensitive for the measurement of different stress levels of a specific task (Nygren, 1991). The NASA-TLX measures subjective stress during processing a working task on six scales, each with a different dimension. These dimensions relate to features of the task (mental, physical, and temporal demand), behavioral characteristics (performance and effort) and individual characteristics (level of frustration). The scales are bipolar with the verbal description of the minima (0) and maxima (20) at the beginning and end points on the scale, so the highest possible score is 21. Following Rubio et al. (2004) the values of all six scales were added and subsequently divided by the number of scales to get an unweighted mean across all scales. Furthermore, all six scales can also be considered individually, to achieve statements about domain-specific stress.

HRV Assessment

As for baseline measurement, subjects were instructed to record their early morning HR immediately after waking up at home. The participants were asked to remain in their bed, after waking up, wear the Polar® belt and record HR for 20 min during rest supine. The supine measurement in the early morning immediately after waking up is considered a valid tool for the detection of the short-term cardiac autonomic control in baseline condition at rest, according to the Task Force of the European Society of Cardiology (1996).

As for the measurements before (pre), during (dur) and after (post) a realistic deployment in a container, systematically set on fire, a sitting posture was maintained for all these three 15 min-long measurements; participants were asked to refrain from any food or liquid immediately before the measurements. Further requirements were the abstaining from alcohol and other drugs at least from the night preceding the experiment, as well as to avoid intensive physical training for at least 24 h before the measurement.

RR-interval series were recorded with a validated cardiac monitor (mod. RS800CX®, Polar Electro Oy, Kempele, Finland), a system consisting of a chest strap and a watch/training computer as data receiver. The analysis of the HRV indices was performed with the software Kubios HRV ver. 2.1 (Tarvainen et al., 2014). The threshold was set to 0.45 s with the "very low" artefact correction algorithm from Kubios software. Records with more than 3% of beats recognized as artefacts were discarded from the subsequent anaysis. To ensure a better quality of the analysis, only the last 10-min segments at the end of the respective recording period were used. This was done to standardize the measurement, after having analyzed some preliminary data, in which a first transient phase of adaptation to the posture and of relaxation was observed. After this phase, the cardiovascular parameters reached a steady state. The last 10 min were therefore selected manually for each recording file in all measurement points (baseline, before, during, and after deployment in the container). During each bout of exercise, HR quickly reached a plateau value: in those few cases in which HR continued to increase monotonously during exercise, we applied a detrending procedures by subtracting the linear trend of HR increase. HRV indices in time domain (RMSSD and pNN50, both indices of parasympathetic activity), frequency domain (High Frequency—HF—power, index of parasympathetic outflow; low frequency—LF—power, which reflects both parasympathetic and sympathetic activity; LF/HF ratio) and in non-linear domain (detrended fluctuation alpha 1—DFA1—the short-term fractal index, which increases when the vagal outflow decreases or the sympathovagal balance is shifted toward sympathetic predominance) were calculated; see **Table 2** for a description of the selected HRV indices.

Experimental Procedure

Twenty male professional firefighters underwent a beat-to-beat HR monitoring at baseline (upon awakening a few days before the experiment, 20 min supine), before, during and after a realistic deployment exercise in a container (15 min sitting), systematically set on fire. In order to compare the workload in the container, participants were randomized into two groups. One group (Ex, $n = 10$) performed a physical exercise in the burning container, whereas the other one remained sitting, without exercising (NoEx, $n = 10$).

On the day of the survey, three measure time points were considered. A sitting posture was maintained for all

TABLE 2 | Selected heart rate variability indices.

Variable	Unit	Description
RMSSD	ms	Root mean square of differences between successive NN intervals. Index of parasympathetic outflow.
pNN50	%	The percentage of successive NN intervals that differ more than 50 ms. Index of parasympathetic outflow.
LF	ms^2	Low frequency power. Index of sympathetic and parasympathetic activity. Ranges from 0.04–0.15 Hz.
LFnu	nu	LF power in normalized units. LF/(Total Power − VLF) × 100.
HF	ms^2	High frequency power. Index of parasympathetic activity. Represents the respiratory sinus arrhythmia. Ranges from 0.15–0.40 Hz.
HFnu	nu	HF power in normalized units. HF/(Total Power − VLF) × 100.
LF/HF ratio		Ratio between LF and HF band powers, which represents sympathovagal balance.
DFA1		In detrended fluctuation analysis, short-term fractal index. DFA1 reflects the sympathovagal balance: it increases as the vagal tone decreases.

NN, normal-to-normal beats, after removing ectopic beats; nu, normalized units.

measurements (**Figure 1**). The measurements without fire contact were carried out in a relaxing area typically used for preparation and instructions. The relaxing area was a covered terrace with benches (ca.15 m^2), 10 m apart of the container.

Before dressing up with the protective gear, participants were equipped with chest strap systems of the cardiac monitor. The training computer was not worn on the wrist, since it was found, that the straps of the gloves over the watch band were uncomfortably tight. Therefore, the watch was placed around the suspenders. Afterward the participants prepared for entering the burning container in usual routine. For safety reasons, the participants were accompanied by an instructor. In order to enable the instructor to monitor the exercises and to keep his workload as low as possible three participants—and four on the last run—completed the exercises in the container at the same time.

15 min preliminary measurement while sitting in the relaxing area was done immediately before entering the container.

The Ex and NoEx groups were given different tasks in the container. The participants of the NoEx group should preferably not move while sitting on wooden pallets and behave calmly inside the container. The Ex group underwent a physical exercise with a home-built rowing ergometer (**Figure 2**). A 26 kg weight was attached to the cable, to simulate, within the limited space inside the container, the average physical workload of a realistic fire extinguishing task.

The general process inside the container was the same for both groups but differed in task definition. The container was set on fire by a study employee in advance. The temperature was achieved by the controlled burning of wood inside a separate booth of the container (**Figure 3**). The combustion was controlled so that the temperature did not exceed 150°C at 150 cm above the ground (roughly at head level while sitting). By reaching this target temperature the participants were accompanied by the instructor into the burning container. They took their places on the wooden pallets in a sequential order. After all participants had taken seat, a 10 min adaptation phase to the heat in sitting posture was provided. At the end of this phase, a 3 s jet of extinguishing water (8 ± 2 L) was released into the cabin to adjust fire intervention. The relative humidity approached 100%, which

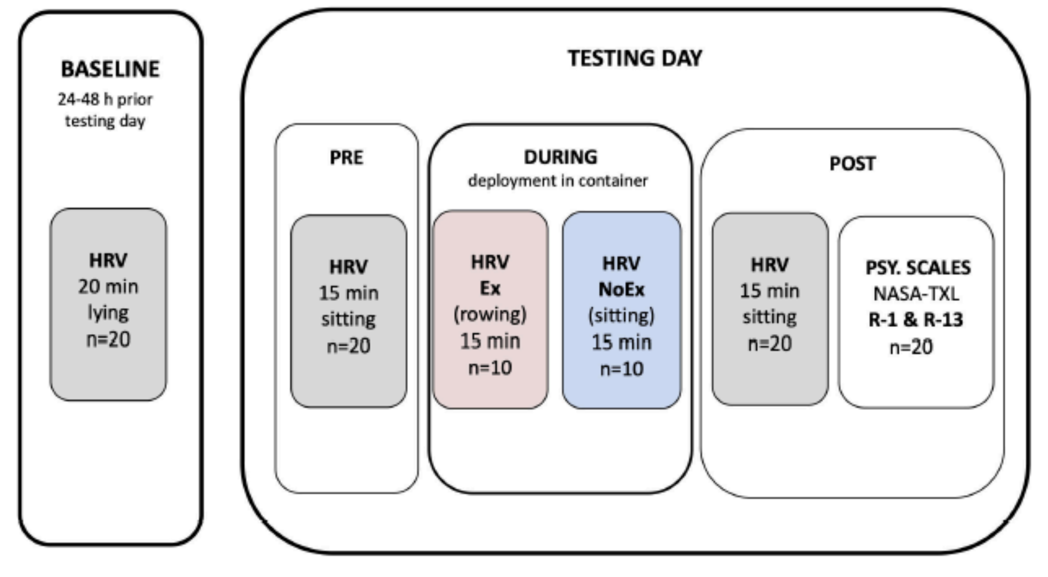

FIGURE 1 | Experimental protocol overview. HRV, heart rate recoding for heart rate variability assessment; PSY. SCALES, psychometric scales conduction.

FIGURE 2 | Self-built rower ergometer. A cuff was attached so that the handle could not be pulled further than 60 cm. The wooden pallet identifies the standardized seating position.

is a common phenomenon in realistic firefighting. After this first extinguishing attempt, the actual exercise for the participants of the Ex group began, while the NoEx group remained sitting calm.

The exercise protocol (Ex group) consisted of 10 rowing trains in five sets. When the first participant finished with his first set (10 arm pulls), he slid on the wooden pallets backward and the next participant started to pull his first set. This was iterated five times, so each participant completed a total of 50 arm pulls. Afterward a 3 s jet of extinguishing water was delivered to the container by the instructor and the participants again completed five runs with the same amount of arm pulls as before. Accordingly, the completion of 100 rowing trains was the exercise goal, 50 trains in dry and 50 trains in damp heat. If a competitor did not manage the moves, he was dismissed by the instructor and if necessary, had to leave the container. An average stay of 16.5 ± 0.2 min in the container was recorded with a stopwatch.

After the practice in the container, the procedure of cooling down was prescribed for both groups. The respiratory protection devices were removed and a 15 min recovery phase while sitting in the relaxing area was performed. Subsequently, the participants were asked to complete the NASA TLX, as well as the psychometric questionnaires R-1 and RS-13.

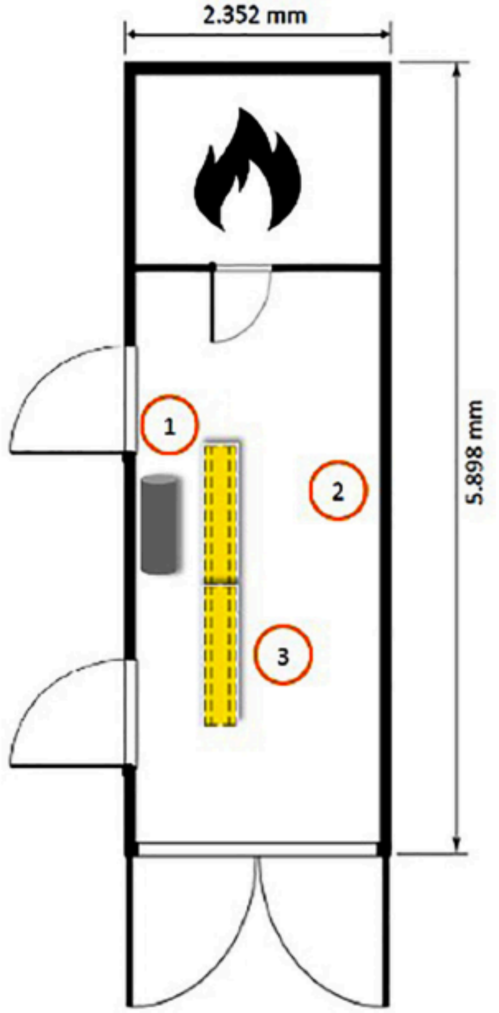

FIGURE 3 | Floor plan of the container. The doors are closed during the exercise. 1. location of the rowing machine, in front of it two stacked seats. 2. location of the experimenter. 3. waiting area for participants.

Statistical Data Analysis

If not otherwise stated, data are reported as mean ± standard deviation ($m \pm$ SD). The statistical analysis was performed with the statistics program R ver. 3.5.2. All data was tested on homoscedasticity (Levene test), sphericity (Mauchly test) and normal distribution (Anderson's Darling test). A logarithmic (log) transformation was applied to frequency domain indices to achieve normal distribution (Castiglioni et al., 1999). As the main outcome of this work was the relationship between HRV and resilience parameters, the sample size calculation has been applied *a priori* to the simple linear regression between a representative parameter of resilience (RS-13) and a representative index of parasympathetic tone (RMSSD) in a small preliminary sample of our subjects. The sample size estimate (power of 80%, two tails t test on linear bivariate regression, a error 0.05) was of 21 subjects (calculated actual power = 0.81).

A repeated multifactorial ANOVA was used to assess the time course of the cardiovascular changes within and between the subjects. *Post hoc* tests according to Tukey HSD were calculated to discriminate between time points and groups. Linear regression analysis was performed to calculate the correlation between the HRV and psychological data. The significance level was set at $p = 0.05$ with confidence interval at 95%.

Due to the standardization of the Risk Scale (R-1), the participants were categorized in age groups. In the present sample, the first age group (18–35 years) consisted of $n = 10$ people and the second age group (36–65 years) also consisted of $n = 10$ people.

RESULTS

Time Course of HRV Indices

Significant differences between the groups in HRmean and in the HRV indices LF, HF and DFA1 could be shown. As expected, the HRmean was significantly higher in the Ex group during ($p = 0.002$; +22 bpm, 95% CI [9.70, 35.82]) and in post—after the deployment ($p = 0.005$; +24 bpm; 95% CI [8.62, 41.16]). Furthermore, the Ex group showed a trend to lower LF ($p = 0.06$; -0.65 ms^2, 95% CI [-0.04, 1.35]) and HF ($p = 0.07$; -0.69 ms^2, 95% CI [-0.06, 1.45]) after exercise. DFA1 showed a significant difference overall between the groups ($p = 0.004$) and specifically in post (**Figure 4**), whereas as for baseline and pre (before entering the container) no significant differences between the groups in all HRV indices were retrieved. Overall, as for RMSSD and pNN50 no significant differences between the groups were found.

HRV and Workload (NASA-TLX)

As for the features of the task *mental demand* and *temporal demand* of the NASA-TLX, correlations could be found. In the NoEx group pNN50 clarifies a significant proportion of the variance of the model with *mental demand*. Forty percent of the variance of pNN50 ($r(8) = 0.402$; $p = 0.04$) is explained by *mental demand*. Furthermore, the indices RMSSD, pNN50 and DFA1 clarify a significant portion of the variance of the model with *temporal demand*. 51% of the variance of RMSSD ($r(8) = 0.509$; $p = 0.02$), 51% of the variance of pNN50 ($r(8) = 0.514$; $p = 0.02$) and 70% of the variance of DFA1 ($r(8) = -0.700$; $p = 0.003$) are explained by the time demand. In the Ex group the behavioral characteristic *performance* clarifies a significant portion of the variance of the model with the indices HRmean, pNN50 and LF. Fifty-four percent of variance of pNN50 ($r(8) = 0.536$; $p = 0.01$), 65% of variance of LF ($r(8) = 0.650$; $p = 0.005$) are explained by performance. The HRmean, is negatively correlated with performance and accounts for 45% of the variance ($r(8) = -0.445$; $p = 0.03$). For the NoEx group the indices LFnu, HFnu, and LF/HF ratio reveal a significant proportion of the variance of the model. Forty-one percent of the variance of LFnu and HFnu ($r(8) = 0.410$; $p = 0.04$), and 57% of the variance of the LF/HF ratio ($r(8) = 0.571$; $p = 0.01$) are explained by the *performance*. The correlation coefficients of the regression analysis provide no significant variance explanation for the model with the total score of the NASA-TLX for both groups. The same occurs for *effort*, *physical demand*, and *frustration level*. For the overall score, as well as for *effort*, more variance components were clarified by the NoEx group. For the *physical demand*, as well as for *frustration* significantly more variance was informed by the Ex group.

HRV and Risk-Taking Behavior (R-1)

In the first age group (18–35 years) the average score for risk-taking behavior was 5.20 ± 0.42 ($m \pm$ SD), which tends to be higher ($p = 0.10$) than the reference sample. Subjects in the second age group (36–65 years) scored on average 4.90 ± 0.73, which is significantly ($p = 0.05$) above the value of the age-specific reference sample (for absolute values see **Table 3**). Therefore, the present sample is more prone to risky behavior than references.

The analysis showed positive correlations for risk-taking firefighters and an increased HRmean at baseline ($r(8) = 0.526$; $p = 0.01$), during ($r(8) = 0.445$; $p = 0.05$) and tendentially post exercise ($r(8) = 0.408$; $p = 0.06$). Significant positive correlations in baseline were also found for the LFnu ($r(8) = 0.353$; $p = 0.05$), the LF/HF ratio ($r(8) = 0.522$; $p = 0.01$), and DFA1 ($r(8) = 0.402$; $p = 0.03$). The latter are also significantly increased in risk-taking firefighters before entering the container (pre) [LF/HF ratio ($r(8) = 0.419$; $p = 0.03$) and DFA1 ($r(8) = 0.562$; $p = 0.02$)]. Significantly negative correlations for risk-taking firefighters were found for the RMSSD in baseline ($r(8) = -0.345$; $p = 0.05$) and pre ($r(8) = -0.445$; $p = 0.05$) and in baseline for the HFnu ($r(8) = -0.353$; $p = 0.05$).

HRV and Resilience (RS-13)

In the present sample, a mean value of 75.76 ± 6.92 of RS-13 was retrieved (for absolute values see **Table 3**), which corresponds to a feature characteristic in the collective lying above the range reported by Schumacher et al. (2005). Significantly positive correlation could be found for RMSSD ($r(18) = 0.288$; $p = 0.04$) (**Figure 5A**). Significant negative correlations were retrieved for logLF/HF measured in the baseline and resilience ($r(18) = -0.289$; $p = 0.04$) (**Figure 5B**) and logLF/HF measured in the pre and resilience ($r(18) = -0.201$; $p = 0.05$) (**Figure 6**); although not significant, a trend toward a negative relationship between DFA1 and resilience was observed.

DISCUSSION

In the present study, relationships between mental states and the modulation of the autonomic nervous system in firefighters during a realistic deployment simulation could be shown. The cardiac response to a fire extinguishing task correlated with both physical and subjective stress levels. To the best of our knowledge, the on-the-spot measurement of a real combustion is a hitherto unique setting. The main results of this study can be thus summarized as follows: first, as expected, physical and psychological stress in a high risk environnment typical in

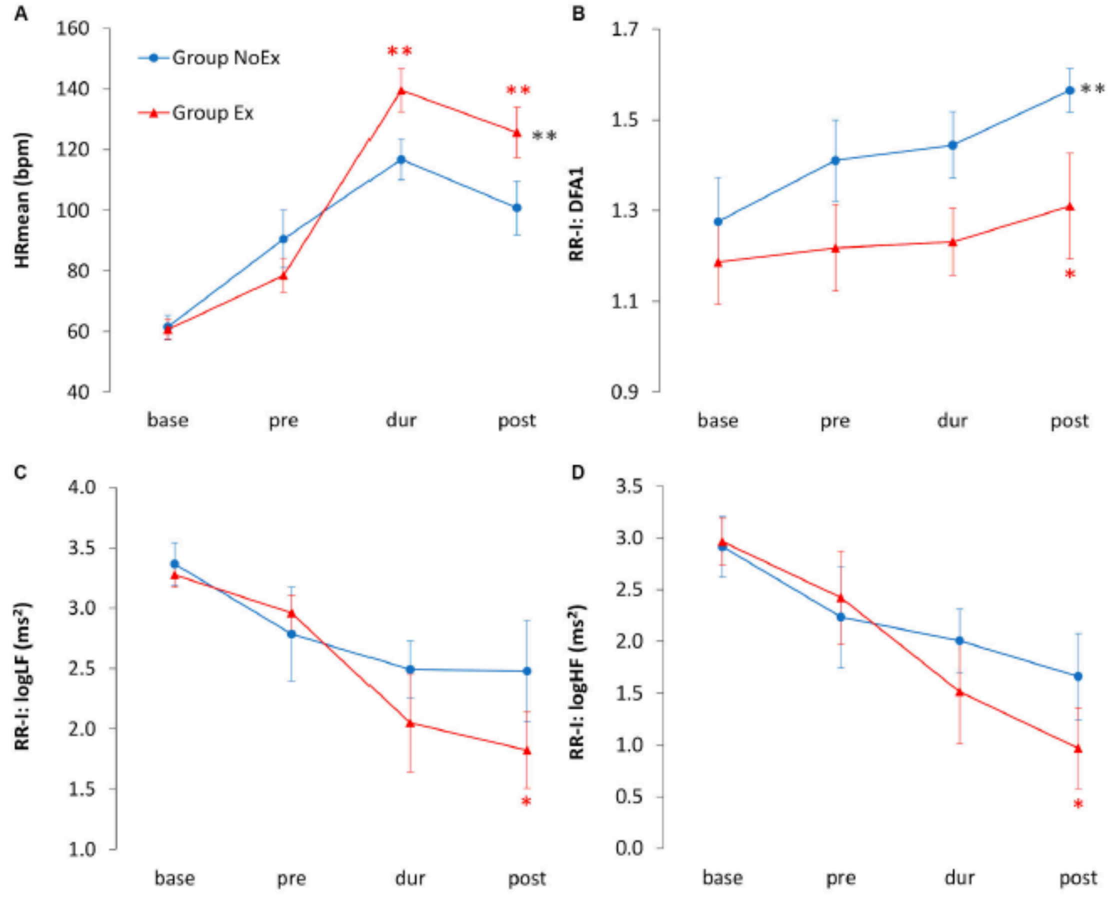

FIGURE 4 | Time course of HRmean and HRV indices. Blue circles indicate the no-exercise group (NoEx) and red triangles indicates the exercise group (Ex). Time of measurements: base, 2 ± 1 days before deployment exercise (baseline); pre, before entering the container; dur, during deployment in the container; post, immediately after deployment. **(A)** HRmean (bpm); **(B)** DFA1 detrended fluctuation alpha 1, index of sympathovagal balance in non-linear domain; **(C)** log LF (ms^2) low-frequency power, index of sympathetic and parasympathetic drive; **(D)** log HF (ms^2) high-frequency power, index of vagal tone. Black asterisks: significance between the groups for each timepoint. Red asterisks: significance between the groups for the respective timepoint. $^{**}p < 0.01$, $^{*}p < 0.05$.

firefighting are reflected by cardiac adaptations, secondly, risk-taking behavior is associated with low vagal outflow and thirdly, resilience is associated with high vagal outflow.

Compared to baseline data, a significant shift in sympathovagal balance toward a sympathetic predominance before entering the container could be demonstrated. This means that preparatory actions as well as psychological stress might be measured by the HRV analysis. As expected, in the burning container, the mean HR in both groups is increased, presumably due to a vagal inhibition and/or a sympathetic system stimulation (the neuro-hormonal aspect of catecholamine incretion, although of interest, was beyond the purpose of this study).

After stress, the HRV reflects the dynamic adjustment of the cardiovascular system during the recovery phase and shows a better sympathetic system reactivation in Ex compared to the NoEx group. It can be suggested that physical strain, as expected, is associated with a withdrawal of the vagal indices of HRV, which is also evident in the recovery phase, when the reverse phenomenon can be perceived.

In addition, the exercise appears to affect data collected in the pre with respect to baseline, since preparatory stress displaces the vagal control. Furthermore, as for baseline and pre data, heat stress without physical exercise also results in a reduction of vagal indices, which could be demonstrated in the NoEx group. The assessment of the subjective stress reflects the effect of the exercise on the cardiac response. As expected, more variance proportions are elucidated in task related dimensions, such as *physical effort*. The higher the perceived *physical effort*, the lower the parasympathetic indices, and the higher the *physical demand*, the higher the HRmean. As for the subjective dimension of *performance and frustration*, the exercise's goal for the Ex group compared to the NoEx group was relatively difficult to achieve. The NoEx group showed significantly positive correlations between parasympathetic drive and *temporal* and *mental demands*. Especially when *temporal demand* was perceived, a sympathovagal balance shifted toward sympathetic predominance could be observed, displaying mental stress processes compared to the Ex group.

In general, the difference between the groups in terms of subjective stress was not as strong as expected. This may have been due to the task sensitivity. The participants of the Ex group were highly motivated to reach the exercise's goal. If the goal was not achieved, the frustration level was correspondingly high. The participants of the Ex group were only able to attribute the success in the task to their own abilities. On the other hand, the exercise's goal for the participants of the NoEx group was quite easy to achieve. The only thing they had to do was sitting calm and watching the instructor to extinguish the fire. For this reason, they could attribute elements of the task to the instructor, so an attribution effect could have affected their subjective rating of the NASA-TLX.

TABLE 3 | Absolute values of the analyzed psychometric indicators for risk-taking behavior and resilience (measured after deployment in the container).

Groups	R-1	RS-13
NoEx	5	82
	4	84
	5	73
	5	86
	5	64
	5	76
	6	80
	4	74
	5	73
	5	78
m ± SD	4.9 ± 0.5	77 ± 6.4
Ex	4	68
	5	84
	5	71
	6	88
	6	73
	6	77
	5	84
	5	69
	5	67
	5	70
m ± SD	5.2 ± 0.6	75.1 ± 7.6
p-value	0.2	0.5

R-1, Risk-taking Scale (Beierlein et al., 2014); RS-13, Resilience Scale, short form 13 items (Schumacher et al., 2005). p-value: between groups.

It becomes clear that the subjective assessment of workload is reflected in the cardiac stress response and that HRV is a reliable tool to differentiate between stress situations. When considering physiological processes in field investigations, respective environmental factors must be considered. In addition to heat stress, nutrition, caffeine, nicotine and other drugs cause a withdrawal of vagal control (Voss et al., 2015). Beside these environmental and lifestyle-related factors, mental illnesses such as depression or anxiety disorders also result in reduced vagal outflow (Henje-Blom et al., 2010; Liddell et al., 2016). Apart from alcohol, other drugs and drug therapies, these factors were not controlled, even though environmental temperature was standardized during deployment. To our knowledge, there are no data in the literature regarding the effect of such acute and high heat stress on HRV, however, results of the acute effect of sauna on HRV are in line with our findings (Leicht et al., 2018).

Results showed that the personality trait risk-taking behavior is significantly associated with a lower vagal outflow in baseline and pre. In risky firefighters, the HRV indices of parasympathetic activity are significantly reduced. The baseline LF power increased, whereas HF powers and other parasympathetic-related indexes decreased, with the propensity towards risk-taking behavior: this suggest a predominance of sympathetic drive in these individuals. A shift toward sympathetic prevalence is also indicated by the significantly negative correlations between risk-taking scale indexes and logLF/HF and DFA1 at baseline and pre. In addition, for high-risk firefighters, the HRmean is higher in the baseline, during the exercise and in the recovery phase. Thus, there is an association between risk-taking behavior and the positive chronotropic effect of autonomic nervous system on the heart. It can be stated that the personality trait risk-taking behavior in firefighters is associated with the modulation of the autonomic nervous system.

The psychological facets of the sample suggest an above-average level of risk-taking behavior and resilience. Theoretical considerations suggest that risk-taking behavior is particularly pronounced in young adulthood (up to the age of 30 years)

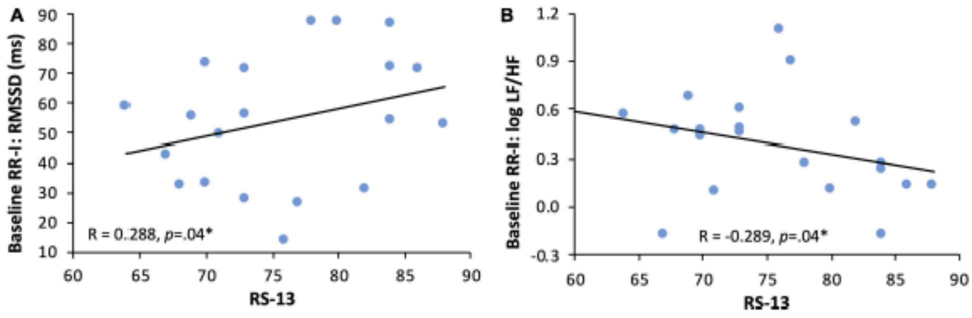

FIGURE 5 | Regression of resilience and HRV indices at baseline. Panel **(A)** RMSSD (ms): root mean square of successive differences between NNs (index of vagal tone) and RS-13 score: short version of Resilience Scale with a score ranging between 13 and 91 (13–66 score: low expression of resilience; 67–72 score: moderate expression of resilience; 73–91 score: high expression of resilience). Panel **(B)** logLF/HF, index of sympathovagal balance in frequency domain and RS-13 score.

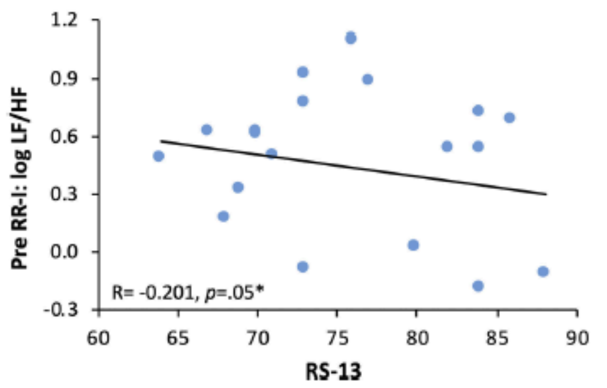

FIGURE 6 | Regression of resilience and logLF/HF at pre. Regression of logLF/HF, index of sympathovagal balance and resilience as RS-13 score (short version of Resilience Scale with a score ranging between 13 and 91 (13–66 score: low expression of resilience; 67–72 score: moderate expression of resilience; 73–91 score: high expression of resilience), before entering the container.

(Josef et al., 2016). Although this is also the case in the present sample, older firefighters (35–65 years) are significantly more prone to risk-taking behavior than age-matched reference groups. One reason could be the working environment of firefighters. For example, the subjective risk assessment and the communication of risks between colleagues and within the regulatory structures lead to a reinterpretation of the risk status, which is reflected in the risk attitude and readiness (McLain, 1995; Rötzel, 2015; Buchholz and Knorre, 2019, pp. 177–198). This reinterpretation of the actual risks can lead to an underestimation of the risks and thus lead to a significantly higher willingness to take risks. In addition, the higher level of experience of the older firefighters could lead to increased risk-taking behavior. However, biological, psychological and social changes cannot be ruled out, so that no causality between the willingness to take risks and the fire service profession can be assumed.

Resilience was significantly associated with vagal indices of HRV in the baseline. The hallmark feature resilience is associated with higher vagal indices of HRV. The baseline relationship observed between logLF/HF and RS-13 scores suggests that resilient firefighters have higher parasympathetic control of the heart than less resilient firefighters. However, as expected, this effect is masked during physical activity.

The deployment was simulated, however, there was still a real source of fire, with real fire gases and correspondingly high thematic loads. Underestimating this situation, although widely controlled, leads to fatal consequences. These results support that the HRV may be useful tool for monitoring firefighters' health and individual fitness not only from physiological point of view, but also for psychological aspects.

Limitations

The calculated sample size could not be kept due to the utilization of the emergency services, the maintenance and repair of the container and climatic conditions. Women are often under-represented in studies on extreme work environments—especially with the fire departments—which makes the future expansion to female participants more relevant.

Furthermore, we decided to include the LF/HF ratio as a marker of a shift toward sympathetic drive, in spite that the meaning of this index is currently controversial (Heathers, 2012).

The classification of homogeneous fitness, experience and age groups also appears to be useful in the analysis of HRV, as significant differences in linear and non-linear indices have been demonstrated when comparing age and gender groups and the fitness level. Thus, a significant loss of variability and complexity of HRV is associated with sex and age (Voss et al., 2015). Due to the size of the sample, we couldn't infer any effects of sociodemographic data on the relationship between HRV results and psychometric data, which need to be investigated in further studies.

CONCLUSION

On one hand, HRV is a tool to monitor cardiovascular fitness, as health-promoting means, disease prevention and to improve cardiac fitness among firefighters. On the other hand, HRV can be used to assess psychological states as well as personality traits. Knowing how psychological aspects are associated with autonomic nervous system modulation, may allow to integrate new personalised reccomendations, which are of crucial relevance, especially in this specific professional group. Therefore, biomarkers as HRV are key elements of personalized diagnostics, therapy and treatment.

HRV is a particularly beneficial technique because the measurement is relatively inexpensive, comfortable and provides qualitative data, at least intra-individually reproducible.

DATA AVAILABILITY STATEMENT

The datasets for this article are not publicly available due to privacy protection reasons. Requests to access the datasets should be directed to the corresponding author.

ETHICS STATEMENT

This study was approved by the Ethics Committee of the Charité University of Medicine Berlin (document number EA4/177/17) and by the Head of Berlin Fire Department. All subjects gave written informed consent in accordance with the Declaration of Helsinki (World Medical Association, 2013).

AUTHOR CONTRIBUTIONS

MM and RP developed the theory, performed the computations, and verified the analytical methods. RP collected the data. OO conceived the idea and provided the project's setting. BG organized the work on site and contributed to data collection. GM encouraged to investigate specific HRV indices and supervised the findings of this work. H-CG supervised the project. All authors discussed the results and contributed to the final manuscript.

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3. Discussion

In the included five papers, cardiac responses to exercise under different special conditions are described. These special conditions are very different, but similar under the benchmark of *extreme*:

1. Neuromuscular progressive untreatable neurodegenerative disability, as MD, and specifically DMD, which affects directly myocardial tissue, inducing weakness and muscle wasting, thus being *extreme,* especially during physical performance, such an electric-wheelchair hockey match. For DMD persons, a real game, is not only physically but also psychologically extremely demanding. The cardiac adaptation to performance, of this *disabled* heart was investigated analyzing also HRV.
2. Physical disability, such as SCI, which is a condition of extreme forced inactivity and thus *extreme* for the cardiovascular system, investigating the *chronic* effects of endurance training on the heart with echocardiography and physical performance test, by assessing $VO2_{peak}$.
3. Long-term bed rest, which imposes not only extreme inactivity, but also the lying position, head-down -6 degrees, continuously for 60 days, thus being *extreme* to the cardiovascular system for the cephalad fluid shift, analyzing effect of high-intensity resistance exercise as a countermeasure.
4. Competing in a subarctic 690 km-long ultramarathon, which means a continuous endeavor of physical high performance in a hostile environment (extreme cold, +5 to -47 °C) for a very long race, sleeping outdoor and being exposed to different stressors, while performing a very physical and psychological demanding task, thus *extreme*.
5. Performing repetitive *exercise* bouts, after a fire extinguish tasks in a container set on fire, facing not only the stress of exercising, but also the *extreme* environmental temperature (up to 150 °C max) and the danger of fire.

The ability of the heart and the cardiovascular system to cope with these extreme conditions could be described and proven. Furthermore, the use of HRV to evaluate the physical performance as well as a monitoring tool appears feasible.

3.1 The disabled and the impaired heart: residual adaptation to performance and training

In the first paper (Maggioni et al., 2008) the acute effects of exercise on the disabled heart were investigated. First of all, it was still unclear whether physical exercise might be beneficial for DMD persons, or on the contrary it might lead to adverse outcomes. Secondly, the residual ability of the heart and cardiovascular system to adapt to the performance was not yet proven. Therefore, even though the workload during a match with an electric-wheelchair may appear quite low, it was of crucial importance in this specific population to observe the cardiac adaptation by recording HR before, during and after the match. Given that the clinical picture of DMD includes genetic mutations yielding to cardiac impairment (Ashwath et al., 2014; Meyers and Townsend, 2019) and disturbances in the electrical conduction, with cardiac autonomic imbalance (Lanza et al., 2001; Inoue et al., 2009; Alvarez et al., 2017), the second aim of this work was to evaluate cardiac autonomic modulation by assessing HRV before, during and after the game. Relevant results are: 1) despite resting tachycardia, there is still a residual capacity to increase HR during physical performance and the extent of this increase appears related to the severity of the pathology; 2) by comparing data with aged-matched healthy peers, the autonomic unbalance at rest (i.e., depressed vagal tone and higher sympathetic drive) was confirmed. Nonetheless, results suggest that the HR increase during the game was due to a parasympathetic withdraw, without increase in sympathetic activity, which probably was already expressed to the upper limit in resting conditions. Indeed, during recovery DMD group showed significantly smaller reduction in HR with respect to OMD, and HRV vagal indices resulted in a very slight increase, supporting the hypothesis that the autonomic failure can critically impair recovery after physical strain. From this point of view, aerobic training, which is known to affect vagal tone, could be beneficial for this specific population. When the work was published, it was one of the first study dealing with the topic of cardiac adaptation to exercise in DMD individuals. In the last years, most studies were focusing on skeletal muscle response to exercise and possible therapies, however it is still unclear whether exercise may overall improve quality of life in these patients (Markert et al., 2011; Kostek and Gordon, 2018), and also guidelines for exercise prescription in these patients could not be yet defined. Probably the introduction of the so-called *Precision Medicine* is the only way to include, under strict monitoring, regular exercise in a therapeutic program for these patients (Kostek, 2019). However, so far no further studies investigated cardiac and autonomic effects of exercise in DMD persons, while recent studies focused mostly on the use of HRV as a tool to define the autonomic imbalance and possibly predict adverse cardiac events (Dhargave et al., 2014; Alvarez et al., 2017; Anderson, 2017; da Silva et al., 2018). The results by Maggioni et al. (Maggioni et al., 2008) appear in line with the data published by the above-mentioned successive studies. Future studies should focus on this specific topic and possibly quantify the individual workload intensity during training in this specific population, which in the present work, due to the characteristic of the performance (i.e., electric-wheelchair hockey game), could not be measured.

In the second paper (Maggioni et al., 2012), the effects of exercise on the heart and cardiovascular system are presented with reference to long-term adaptation, considering here an *impaired* heart, and possibly a *disabled* heart, given that in SCI, with a lesion level above the 6th thoracic vertebra the heart innervation is compromised (Jacobs and Nash, 2004; de Groot et al., 2006; Haisma et al., 2006; Theisen, 2012; West et al., 2015). However, in SCI we are definitely always observing an *impaired* heart, as baroreceptor feedback and vasomotor control in the lower peripheral body districts are absent or compromised, leading to the phenomenon of *blood pooling*, also exacerbated by the absence of the *muscular pump* (i.e., lower limbs muscle contractions), which normally contributes to the venous return. The peripheral *blood pooling* lowers in turn the diastolic volume in the heart chambers, resulting in a severe reduction of the stroke volume. This persistent condition may chronically generate myocardial tissues damages and a decreased functional capacity of the cardiovascular system. Therefore, the definition of the long-term endurance training effects in SCI persons, as a physiological model of impaired cardiovascular system, following *extreme* (forced) physical inactivity and cardiovascular deconditioning, can provide evidence of efficacy to counteract and possibly revert the debilitative cycle. The data from this study showed clearly that, despite the overall functional performance capacity of trained SCI halved the averaged values of able-bodied peers, it still doubled in comparison to untrained SCI. Furthermore, over the time no adverse outcomes were retrievable. Specifically, the observed significant positive correlation between aortic flow velocity and peak oxygen consumption, indicates that despite the performance impairment due to the reduced stroke volume, training could increase heart functional capacity, confirming that a reserve margin to improve remained available, which can be elicited by aerobic training. Heart morphological changes retrieved in trained SCI mimic the changes observed in able-bodied athletes, but to a lesser extent, again supporting the ability to counteract adverse cardiovascular outcomes related to SCI. Exercise can therefore reduce the risk of CVDs among this specific population and improve quality of life (Jacobs and Nash, 2004; Hicks et al., 2011; Sandrow-Feinberg and Houlé, 2015). Following studies partially confirmed and supported these finding (Farrow et al., 2020), toward a definitive inclusion of a structured physical exercise program in the routine of SCI persons, by defining the most effective training protocol, which should include also high-intensity exercise (Astorino et al., 2020; Todd et al., 2020).

3.2 Exercise as a countermeasure for cardiovascular deconditioning

The cardiovascular condition following SCI shares some features with the cardiovascular outcomes after long-term bed rest and spaceflight, like cardiac atrophy (Perhonen et al., 2001; Dorfman et al., 2007; Scott et al., 2011; Williams et al., 2019), which may be referred to ANS alterations, forced inactivity and lacking mechanical load. The head-down bed rest research setting has been developed as an Earth analog for space flight (Besnier et al., 2017a), to study cardiovascular adaptation induced by microgravity exposure. One of the characteristic features of this specific bed rest is to mimic on Earth the cardiac unload and the cephalad fluid shift observed in weightlessness, by adding a head down -6 degrees to the horizontal bed rest (Hargens and Vico, 2016; Ried-Larsen et al., 2017). Therefore, the mechanisms underlying similar cardiovascular adverse outcomes, like cardiac atrophy and orthostatic intolerance, may be different with respect to SCI, but definitely related to the absence of mechanical stimulus and forced inactivity. Results from bed rest studies have been very useful also in the clinical practice, especially in the field of post-traumatic and cardiac rehabilitation, to improve therapeutic intervention in efficiently recovering functional capacity (Topp et al., 2002; Hides et al., 2017; Lambrecht et al., 2017). Among healthy individuals long-term head down tilt bed rest represents an *extreme* condition for the cardiovascular system, leading to hemodynamic and autonomic (reversible) consequences, which are summarized in the definition of *cardiovascular deconditioning*. Features of *cardiovascular deconditioning* are resting tachycardia and orthostatic intolerance, also observed among astronauts returning to Earth. One of the crucial tasks to foster manned spaceflight, especially in light of the upcoming mission to Mars, is the development of an effective and time-saving countermeasure not only for the musculoskeletal system, but also for the cardiovascular consequences of micro- and zero gravity, which could lead to impairment in several other functions, bounded to the cardiovascular system, as for example diuresis, fluid balance, brain perfusion. In the third paper this issue was addressed: a countermeasure primarily designed to maintain musculoskeletal trophism and functionality during bed rest was analyzed in its effects on the cardiovascular system. Lessons learned from previous space missions and bed rest studies demonstrated that physical training is one of the most effective countermeasures. Unfortunately, it requires for crewmembers daily sessions, with a large amount of time dedicated only to this task (Hackney et al., 2015; Hayes, 2015; English et al., 2020), and subtracting time to operational duties and scientific experiments. Therefore, scientists are constantly developing training programs to improve the *cost* (time) *benefit* (fitness level) ratio. In this paper a new proposed training tool has been investigated: reactive jumps, performed on a sledge with hydraulic resistance (Kramer et al., 2010, 2017a, 2017b; Maggioni et al., 2018). During 60-day bed rest the treatment group underwent a high-intensity short-duration training protocol, 4-5 times/week, 20 min/session. The hallmarks of this program were *efficacy*, referring to the muscle and bone mineral loss, and *timesaving* for participants. The countermeasure was not expected to mitigate directly the cardiovascular deconditioning, as it consisted in a purely resistive high-intensity and short-duration exercise, besides involving abdominal and lower limbs musculature only. Nevertheless, results from Maggioni et al. (Maggioni et al., 2018) showed clearly how such exercise intervention could mitigate some of the adverse outcomes related to cardiac autonomic modulation and to improve recovery. Specifically, two body positions (i.e., supine vs. sitting) were tested before and after bed rest, enabling the analysis of the cardiovascular dynamic adaptation to the stimulus of body posture change. The training protocol exerted a direct effect on the cardiac autonomic modulation, by contrasting the parasympathetic depression known to occur during bed rest and persisting during recovery immediately after bed rest, with higher resting HR in supine position, which here was shown by the control group only. The introduction of this specific training protocol, starting with low but progressively increasing workloads, may efficiently counteract not only muscle and bone mineral losses, but also cardiovascular deconditioning. This is an important finding for astronauts training programs for future deep space missions, as it saves astronauts' time, for a very high *time-efficiency* ratio. On the other hand, the efficacy of such high-intensity, short-duration, resistance training in contrasting cardiovascular deconditioning is of crucial meaning for rehabilitation programs, fostering the inclusion of resistance exercise in clinical protocols: resistive high-intensity, short-duration exercise *may* and *should* be integrated in rehabilitation programs for post-traumatic and cardiologic rehabilitation, and to improve fitness in older adults.

3.3 Performance in the extreme: HRV in integrating physiology and psychology

Focusing on healthy, well-trained, non-professional endurance athletes, in the fourth paper (Rundfeldt et al., 2018) the cardiac adaptation during long-duration physical performance in an hostile, thus *extreme,* environment was investigated. The unique conditions of this specific race, *The Montane Yukon Arctic Ultra (YAU)*, allow the evaluation not only of cardiac response, but also of psychological correlates, playing the mind a central role in facing these different stressors. Indeed, the racetrack unfolds through the Yukon Territory in Canada, during winter, for 690 km, and includes only two checkpoints for indoor recovering across the whole track. Therefore, competitors during the race must sleep regularly outdoor into the wild and be completely self-sustained. The hallmark of this competition comprises not only extreme physical demanding tasks, such running alone in the snow by carrying in a sledge all the necessary to survive, but also psychological high demanding tasks, such facing wild animals (wolves), sleeping alone outdoor in the forest, keeping constantly the track and maintaining always a clear mind. Participants to the YAU were well trained and experienced marathon runners, however they must face here a multi-folded stress: strenuous and long-duration physical effort, an extreme cold and hostile environment, loneliness and possibly poor sleep quality. Cardiac autonomic modulation, analyzed by HRV, has been proven a reliable tool to assess training efficacy and fitness level (Buchheit et al., 2010; Buchheit, 2014b). Specifically, short-term resting HRV in supine position, upon awakening, is considered a reference value of the individual cardiac autonomic balance (Plews et al., 2013; Buchheit, 2014a), thus could track changes following training/performance or different stressors. At the same time, HRV has been found a marker of psychological stress and resilience, reflecting the individual capacity to adapt and cope with different environments and stressors (Thayer et al., 2009, 2012; Carnevali et al., 2018; An et al., 2020; Perna et al., 2020). Therefore, aim of this study was to test the use of HRV as a tool to predict/monitor the performance considering fitness level and, at the same time, as a marker of psychological correlates. Indeed, several papers already investigated the interplay between ANS and psychological wellbeing or disease (Grippo et al., 2012; Sgoifo et al., 2014, 2015). To test this hypothesis validated psychometric scales were administrated, to look for correlations with HRV indices. The main findings of this study confirm the hypothesis that HRV could be an informative tool for endurance performance. Successful runners showed a dynamic capacity to accelerate the recovery of the depressed vagal tone already during the race (after the first part of the competition), and thus to proceed successfully toward the finish line. Conversely the vagal depression retrieved among competitors who did not complete the race was to some extent greater and probably could not be effectively counteracted. These results are also in line with literature data (Gratze et al., 2005; Buchheit, 2014a). However, here the most interesting finding is that psychological correlates and wellbeing, analyzed by the POMS scale, showed how only those competitors who completed the race, were able to face and cope with the multi-folded stressors already at the very beginning of the YAU. Similar results were retrieved regarding cardiac autonomic modulation, with respect to vagal tone. Considering the characteristics of this in-field study, which impose some constraints, but at the same time offered a unique setting to observe human adaptation to the *extreme*, these findings taken together support the theory of HRV as a marker of fitness level and psychological aspects under these particular conditions; however, further studies are warranted to clarify the underlying mechanisms.

In the fifth paper, the cardiac responses to exercise in the *extreme* in healthy individuals are further investigated, including psychological traits (Prell et al., 2020). Cardiac autonomic modulation at baseline and during physical strain, following a fire extinguish tasks in a container set on fire, as well as resilience and risk-taking behavior were analyzed. Participants were officers of the fire brigade in Berlin, who, as part of their regular preparation activity, must train simulating an emergency situation, by means of extinguish-fire task in a dedicated container. In this scenario, the *extreme* is defined by hot environment (up to 150 °C) and extremely dangerous situation, as facing a fire that must be handled in the shortest time possible. Risk-taking behavior and resilience are key features for these professionals, because they must face continuously dramatic situations, which are extremely demanding not only considering physical strain, but especially regarding psychological aspects, dealing with emergency and life-threatening events; it is crucial for them to be able to quickly evaluate unexpected situations and strategically plan effective countermeasures to design anytime the suitable intervention. Not only at the beginning of their career, but also over the time, with professional experience and aging, it may be crucial to assess physical residual capacity and at the same time resilience and risk-taking behavior. These psychological traits are traditionally assessed via interviews and questionnaires only. In this sense, the study aimed at evaluating the use of HRV as a monitoring tool which integrates cardiac response, physical fitness, and concurrently psychological traits. As previously reported, there are already studies on the use of HRV to assess resilience, but the literature is scarce about this specific population and particularly with respect to risk-taking behavior. Furthermore, so far few studies investigated cardiovascular health among fire-fighters, referring specifically to the perspective of occupational medicine and prevention (Banes, 2014; Hunter et al., 2017; Palmer and Yoos, 2019), whereas in the present paper cardiac responses in the *acute*, i.e., during an extreme situation, inside a container set on fire, are analyzed, including the comparison between exercise and rest. Given that this hot and dangerous environment already poses for the cardiovascular system a severe stress factor, which induces an increase in HR even at rest, here the residual capacity to match the demands of the additional strain of physical effort was investigated and could be demonstrated. Furthermore, the possible association between HRV indices of vagal tone with resilience and risk-taking behavior was analyzed. Results confirmed the hypothesis of a correlation between cardiovagal modulation at rest and resilience and risk- taking behavior: the higher the vagal tone at morning upon awakening, the higher the resilience score and the lower the propensity toward risks. Therefore, these findings support the value of including HRV assessment, together with other evaluation means, in the selection procedure of fire-fighters, as well as a monitoring tool during their professional activity.

4. Summary

The human heart is an amazing hydraulic pump that pushes a non-Newtonian fluid in a system of non-rigid vessels millions of times over the course of a lifetime. The mechanic work of this pump is finely regulated by a complex electrical structure that operates with sophisticated feedback systems. These latter are equipped with peripheral sensors and central and peripheral effectors, in order to ensure that the blood flow to all the body systems is sufficient to satisfy the various basic metabolic needs of life, and to supply of adequate energy necessary for the completion of any external work.

The muscle activity required by physical exercise, which goes from simply get up from a chair in an elder to preserve the autonomy at home, to the performance of an ultra-marathon runner, finalized to complete a race against extreme environmental conditions, represents the most important physiologic stress for the heart. To cope with the exercise challenge, the cardiovascular system must be therefore able to adapt its performance ranging from a minimum activation level to the capacity of supporting for long time the maximum cardiac output. Amazingly, the physical work required by the exercise to the heart can be done in a cardiovascular continuum of performance that goes from the diseased heart (as in heart failure and primarily cardiac diseases) to the trained heart of the elite athlete. The five articles reported in this dissertation are linked by an important *fil rouge*: the ability of the cardiovascular system to cope with extreme conditions, in which the exceptional nature of the stimulus is due to very different factors: for a pathology that directly compromises the heart's response to exercise, the light muscle movements necessary to move an electric-wheelchair can be very "demanding" for the cardiovascular system, while for the trained heart the physical activity requested in conditions of extreme environment underlines an adaptation ability near to the tolerable limits of human possibilities.

Throughout this continuum of cardiovascular performance of the human heart, the interaction between the environment (simple daily relation life, microgravity, extreme ambient conditions) and the cardiac response to exercise highlights very close links between the heart and the main control system of its mechanical action, the autonomic nervous system, which represents one of the most ancestral (and thereby important) parts of the entire nervous system.

In all the conditions in which the cardiac performance was studied in these five articles, it was important to be able to measure as directly and simultaneously as possible both, the cardiac internal load during exercise and the efficiency of its main neural control factors. In these papers it is shown how, despite the extreme variability of environmental stimuli and the stressful factors that influence the cardiovascular system, HR and HRV represent two adequate tools for synchronously assessing cardiac performance on the one hand and the efficiency of his autonomic control during physical exercise on the other. Furthermore, in some study conditions depicted in these articles, physical stress was also added to mental/psychologic stress: again, the HRV tool proved to be adequate in describing the heart's response to these types of non-muscular stress on the heart.

If one considers that this monitoring system is absolutely non-invasive, that it can be analyzed starting from a single biological signal (the electrical activity of the heart), that it easy to use, that does not require sophisticated and expensive instruments, its usefulness in evaluating the adaptability of the heart, both pathological and trained, to the continuous "challenges" that the cardiovascular system has to face is clear.

Nevertheless, some aspects are still to be evaluated and will require further studies about the use of these analysis systems: for example, i) finding more correct descriptors of the sympatho-vagal balance, ii) better exploring the non-linear components of the cardiac signal, aiming at evaluating the responses of the systems that do not depend on simple action-reaction feedback mechanisms, iii) assessing new ECG signal descriptors that are more directly correlated with the mechanical characteristics of the heart, iv) evaluating the efficiency of new HR and HRV monitoring systems that do not require the strict processing of the cardiac electrical signal (such as the vascular photoplethysmography), v) evaluating the determination capacity of these analysis tools with respect to the onset of fatigue during a continuous recording, vi) better focusing on the crucial relationships between cardiac and respiratory activity, vii) evaluating the effects of senescence both on the mechanical part and on the autonomic control of the heart, are just some of the several challenges that we will face in the next years.

However, I believe that the results obtained so far are very promising and I hope that this field of investigation can be deepened and enriched with new methods to evaluate the cardiovascular efficiency during exercise, especially by expanding the prognostic capabilities of these measurements in the field of cardiovascular pathologies, which is still one of the most important health issues to be addressed in the near future.

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7. Eidesstattliche Erklärung

§ 4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass

- weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wurde,
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- mir die geltende Habilitationsordnung bekannt ist.

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