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Relationship between combat-related traumatic injury and ultrashort term heart rate variability in a UK military cohort: findings from the ADVANCE study

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ABSTRACT

Introduction Combat-related traumatic injury (CRTI) has been linked to an increased cardiovascular disease (CVD) risk. The long-term impact of CRTI on heart rate variability (HRV)—a robust CVD risk marker—has not been explored. This study investigated the relationship between CRTI, the mechanism of injury and injury severity on HRV.

Methods This was an analysis of baseline data from the ArmeD SerVices TrAuma and RehabilitatioN OutComE (ADVANCE) prospective cohort study. The sample consisted of UK servicemen with CRTI sustained during deployment (Afghanistan, 2003–2014) and an uninjured comparison group who were frequency matched to the injured group based on age, rank, deployment period and role in theatre. Root mean square of successive differences (RMSSD) was measured as a measure of ultrashort term HRV via <16 s continuous recording of the femoral arterial pulse waveform signal (Vicorder). Other measures included injury severity (New Injury Severity Scores (NISS)) and injury mechanism.

Results Overall, 862 participants aged 33.9±5.4 years were included, of whom 428 (49.6%) were injured and 434 (50.3%) were uninjured. The mean time from injury/deployment to assessment was 7.91±2.05 years. The median (IQR) NISS for those injured was 12 (6–27) with blast being the predominant injury mechanism (76.8%). The median (IQR) RMSSD was significantly lower in the injured versus the uninjured (39.47 ms (27.77–59.77) vs 46.22 ms (31.14–67.84), p<0.001). Using multiple linear regression (adjusting for age, rank, ethnicity and time from injury), geometric mean ratio (GMR) was reported. CRTI was associated with a 13% lower RMSSD versus the uninjured group (GMR 0.87, 95% CI 0.80–0.94, p<0.001). A higher injury severity (NISS ≥25) (GMR 0.78, 95% CI 0.69–0.89, p<0.001) and blast injury (GMR 0.86, 95% CI 0.79–0.93, p<0.001) were also independently associated with lower RMSSD.

Conclusion These results suggest an inverse association between CRTI, higher severity and blast injury with HRV. Longitudinal studies and examination of potential mediating factors in this CRTI-HRV relationship are needed.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The adverse impact of acute trauma on heart rate variability (HRV) has been reported previously; however, the long-term impact of combat-related traumatic injury (CRTI) on HRV remains unexplored.

WHAT THIS STUDY ADDS

⇒ We found that CRTI, injury severity and blast injury were independently associated with lower root mean square of successive differences (RMSSD)—a measure of HRV.

⇒ This is the first study to report lower RMSSD (indicative of autonomic imbalance) among injured servicemen in comparison with frequency-matched uninjured servicemen using the data from the ADVANCE (ArmeD SerVices TrAuma and RehabilitatioN OutComE study, UK.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings may present implications for military practice and policy by providing evidence on CRTI-HRV relationship to inform, design and develop interventions for rehabilitation.

INTRODUCTION

Combat-related traumatic injury (CRTI) has been known to cause adverse psychophysiological health outcomes in servicemen. Among a myriad of medical conditions reported in combatants who have sustained CRTI, there is evidence to suggest its association with future cardiovascular disease (CVD) risk.[1] This evidence has been strengthened following more contemporary observational data from the recent wars in Iraq and Afghanistan (2003–2014).[2 3] Recent studies have shown that CRTI is linked to increased systemic inflammation, arterial stiffness, metabolic syndrome,[2] hypertension and coronary artery disease.[3] Furthermore, in these studies, the cardiovascular risk profile was more adverse with worsening injury severity.

The measurement of heart rate variability (HRV) offers new possibilities to explore the relationship between CRTI and CVD risk. HRV is a non-invasive measure of autonomic balance and function[4] and is a robust biomarker of CVD risk; reduced HRV has been consistently linked to a wide range of adverse outcomes including metabolic syndrome,[5] poor mental health[6] and increased systemic inflammation[7] in both healthy and patient populations. In the acute trauma setting, lower HRV has evolved as a useful ancillary marker of injury severity and sympathetic dominance, and is related to worsening outcomes including all-cause mortality.[8 9]

The measurement of HRV has traditionally involved the quantification of changes in the

cardiac interbeat interval (IBI), acquired with electrocardiography (ECG), over a minimum recording period of 5 min.[4] With advances in technology and associated software the utility of much shorter recording periods of under 2 min—known as ultrashort term HRV (HRV_{UST})—and IBI acquired using differing arterial (eg, brachial, radial and capillary) waveform data have been validated.[10 11] This has created potentially important translational research and clinical applications owing to their simpler acquisition and improved patient comfort versus traditional HRV measures. Of current HRV_{UST} measures, the root mean square of successive differences (RMSSD) between normal heartbeats is the most validated and has shown strong agreement with RMSSD values from standard ECG-derived HRV recording periods of >5 min.[12 13]

The longer term effects of CRTI on HRV have not been investigated to date. In this study, we primarily sought to explore, for the first time, the association between CRTI and HRV_{UST} among a contemporary population of military personnel and veterans. Our secondary aim was to explore the impact of injury severity and mechanism on HRV_{UST}. We hypothesised that HRV_{UST} would be lower in the injured group compared with a frequency-matched uninjured group and further attenuated by injury severity.

METHODS

Study design and setting

This study undertook a baseline analysis of the ArmeD SerVices TrAuma RehabilitatioN OutComE study (ADVANCE) prospective cohort study. The protocol of the ADVANCE study with further details has been previously published.[14] Participation in the study was voluntary and all participants provided informed written consent. The data were collected at Headley Court (March 2016 to August 2018) or at Stanford Hall (August 2018, onwards) following the closure of Headley Court. The ADVANCE study has full ethical approval from the Ministry of Defence Research Ethics Committee (protocol no: 357/PPE/12).

Study population

The participants were male military personnel who served in the UK Armed Forces during the UK-Afghanistan War (2003–2014). The participants were recruited against set inclusion and exclusion criteria. The injured group was defined as servicemen who experienced physical CRTI during their deployment to Afghanistan that required aeromedical evacuation and subsequent hospital admission in the UK. The comparison group was defined as servicemen who were deployed to Afghanistan but were not injured, and were frequency matched to injured participants based on age, service, rank, regiment, deployment period and role in theatre. Participants with a history of CVDs, liver or renal conditions were excluded.[14]

Sample size

The sample size used for the present study represented 862 (75.3%) participants from the full ADVANCE cohort (n=1144) and represented the total number of participants with full disclosure of arterial waveform data, required to calculate HRV_{UST}. The current data were consistent with the original ADVANCE data set with no significant differences in the key demographics and military characteristics (data not shown but available from the authors).

Data collection

The participants refrained from eating and drinking 8 hours before the assessment. The calculation of the IBI to quantify HRV was obtained from arterial waveform data captured and stored during the measurement of pulse waveform velocity using the Vicorder device (Skidmore Medical, Bristol, UK) as previously described and validated.[14 15] Measurements were recorded in a temperature and noise-controlled room. The participants were positioned in the supine posture on a hospital bed with their heads raised to 30°. The latter allowed the relaxation of the skin and muscles overlying the carotid artery.

A 30 mm plethysmography-based partial inflatable sensor was placed over the neck (carotid artery) and a 100 mm wide BP cuff was placed over the left thigh (femoral artery) to sample carotid-femoral arterial waveforms simultaneously in sequential triplicate. All recordings were taken ipsilaterally unless impossible due to amputation (alternatively contralateral recordings).[14] A continuous recording of femoral arterial waveforms over a period of 16 s was used to calculate IBI, HR and HRV_{UST} measure of RMSSD.

Data processing and analysis

All arterial waveform data were imported into the Kubios HRV package (Kubios Premium V.3.2, The Biomedical Signals Analysis and Medical Imaging Group, University of Kuopio, Finland). Erroneous waveforms suggestive of likely ectopic or misplaced beats were excluded as previously described.[16] The following operations were selected for data processing in Kubios: the smoothness priors (500), interpolation (cubic spline: 4 Hz with 50 ms R-R threshold),[16] no automatic correction, medium noise levels and single (for signal length >10 s) or merge analysis type (for signal length <10 s). All analyses of HRV_{UST} were blinded to the participant grouping (injured vs uninjured). The blinded interobserver (n=50; RM and CJB) coefficient of variance was 2.13±6.17% (95% CI 1.06–3.20) and intraclass correlation coefficient was 0.99 (95% CI 0.994–0.997).

Study variables

Combat injury (yes or no), injury severity and injury mechanism were the main exposure variables. Injury severity was quantified using the New Injury Severity Scores (NISS)[14] which range from 1 to 75. The NISS—calculated from the Abbreviated Injury Score (AIS) (2008 update)—uses the sum of squares of the three most severe injuries irrespective of the body region injured.[17] The AIS for NISS calculation were provided by the UK Joint Theatre Trauma Registry which is a collective database of every service casualty admitted to a deployed UK medical facility. NISS was categorised as severe (≥25) and less severe (<25) based on previous data demonstrating the relationship between injury severity and all-cause mortality.[17] Injury mechanism was characterised as blast and other (including gunshot wounds, assaults, burns, etc).

For the outcome measure, only RMSSD from the time-domain measures of HRV was included given its established reliability and validity in HRV_{UST} analysis.[12 13]

Rank at sampling was used as a proxy for the socioeconomic status of the participants as previously described.[2 18] The ranks were classified as lower (junior non-commissioned officers and other lower ranks), middle (senior non-commissioned officers) and senior (commissioned officers). Ethnicity was defined into two categories: White and other ethnic groups.

Statistical analysis

The results are presented as mean and SD for normally distributed data or median and IQR for skewed data. Normality of continuous data was assessed by the visual inspection of histograms and Q-Q plots. Parametric or non-parametric equality tests were used to assess the baseline differences between the injured and uninjured groups as appropriate. Multiple imputation was considered to address the missing data; however, except for the outcome data, the number of missing values was negligible (injury mechanism=1, and time from injury=2). Multiple imputation on the outcome provided no additional information and therefore was handled by default complete case analysis.

Three separate multiple linear regression models were constructed to assess the relationship between HRV_{UST} and CRTI, injury severity and injury mechanism while adjusting for a priori confounders (age, rank, ethnicity, time from injury/deployment to assessment) for each model. Given that RMSSD was positively skewed, RMSSD was log transformed in the models and the coefficients exponentiated to give geometric mean ratios (GMR)—a ratio of two geometric means—for interpretation.

The significance level was set at $p<0.05$. All statistical analyses were conducted in Stata V.15.0 (StataCorp, College Station, Texas, USA).

RESULTS

Sample characteristics

Of the 862 participants, 428 (49.6%) were injured [including 133 (31.1%) amputees] and 434 (50.3%) were uninjured. The overall mean age at assessment was 33.9±5.4 years (range 23–59 years). The mean time from injury/deployment to assessment was 7.9±2.05 years. There were no significant differences between injured and uninjured servicemen in terms of age at assessment, ethnicity, smoking, family history of CVD, height and weight (Table 1).

Overall, 33.9% of injured servicemen had an NISS of ≥25. Blast was the predominant mechanism of injury (76.8%) (Table 1). NISS was higher in the blast injury group compared with other mechanisms of injury (14 (6–27) vs 9 (5–17), $p<0.001$), respectively.

Table 1 Baseline demographics and anthropometric data among uninjured and injured (CRTI)

	Uninjured	CRTI	P value*
n (%)	434 (50.35)	428 (49.65)	–
Age at assessment (years)	33.97±5.46	33.87±5.41	0.80
Rank (%)			
Junior	265 (61.06)	295 (68.93)	0.04
Middle	108 (24.88)	82 (19.16)	
Senior	61 (14.06)	51 (11.92)	
Still serving in military (%)	381 (87.79)	122 (28.50)	<0.001
Time from deployment/injury to assessment (years)	7.87±2.02	7.95±2.08	0.54
Injury mechanism (%)			
Blast	–	328 (76.81)	
Others		99 (23.19)	–
NISS 2008 (IQR)	–	12 (6–27)	–
NISS 2008 (IQR) and injury mechanism			
Blast	–	14 (6–27)	–
Others		9 (5–17)	
Ethnicity (%)			
White	399 (91.94)	385 (89.95)	0.31
Other	35 (8.06)	43 (10.05)	
Smoking (%)			
Current smoker	99 (22.81)	89 (20.79)	
Ex/non-smoker	335 (77.19)	339 (79.21)	0.47
Family history of CVD† (%)	81 (18.66)	76 (17.76)	0.73
Height (cm)	178.93±6.22	179.25±7.32	0.48
Weight (kg)	87.71±12.20	86.64±14.75	0.24
BMI adjusted for amputation (kg/m^2)	27.37±3.37	28.05±4.04	<0.01

Data presented as mean±SD or number (%) or median (IQR) for highly skewed data.
*Based on the comparison of CRTI versus uninjured groups.
†Defined as a history of stroke or transient ischaemic attack or confirmed coronary heart disease in one or more first-degree relatives.
BMI, body mass index; CRTI, combat-related traumatic injury; CVD, cardiovascular disease; NISS, New Injury Severity Score.

Association between CRTI, injury severity, and injury mechanism and HRV_{UST}

Participants with CRTI had a significantly higher resting HR than uninjured participants ($p<0.001$). RMSSD was significantly lower in injured versus uninjured participants (39.47 ms vs 46.22 ms, $p<0.001$). No difference was observed for brachial systolic and diastolic BPs (Table 2).

After adjustment for confounders, injured servicemen had a 13% lower geometric mean RMSSD than those who were uninjured (GMR 0.87, 95% CI 0.80–0.94, $p<0.001$). RMSSD was 22% lower with severe injury (NISS ≥25) and 10% lower among the less severely injured (NISS <25) versus uninjured after adjustment for confounders (Table 3). Blast injury was associated with 14% (95% CI 0.79–0.93) lower RMSSD values compared with the uninjured group. Other mechanisms of injury were not significantly associated with lower HRV ($p=0.15$) (Table 3 and Figure 1).

Increasing age and lower rank were independently associated with lower RMSSD. There was no association between HRV_{UST} and time from injury and ethnicity (Table 3).

DISCUSSION

To the authors' knowledge, this is the first study to investigate the longer term relationship between CRTI, its severity and its mechanism with $HRV_{UST.}$ The findings suggest that CRTI is associated with lower HRV_{UST} compared with that of a frequency-matched comparison group of uninjured personnel who experienced the same operational environment at a similar time. Severe injury (NISS ≥25) and blast mechanism of injury were independently associated with lower RMSSD (HRV_{UST}).

RMSSD is a well-validated HRV_{UST} measure.[12 13] Compared with several other HRV measures, RMSSD is less prone to changes in respiration with a lower value being reflective of depressed vagal function.[19] Lower RMSSD reflects relative lower parasympathetic tone[19] and would help explain the observed higher resting HR among the injured versus uninjured in our cohort.

Given the paucity of research on CRTI and HRV_{UST}, our findings lack a direct comparison with other studies. We have previously reported a significant association between CRTI and resting HR, metabolic syndrome, arterial stiffness (central augmentation index)[2] and post-traumatic stress disorder (PTSD).[18] Moreover, metabolic syndrome,[5] increased arterial stiffness[20] and PTSD[6] have all been shown to be independently

Table 2 Comparison of haemodynamic and ultrashort term HRV (HRV_{UST}) between uninjured and injured (CRTI)

	Uninjured	CRTI	P value*
HR (BPM)	51.85±7.46	54.85±8.91	<0.001
Brachial systolic BP (mm Hg)	131.27±11.49	130.24±11.21	0.18
Brachial diastolic BP (mm Hg)	72.72±8.11	72.63±8.65	0.87
Brachial end systolic pressure (mm Hg)	113.9±11.72	113.2±11.93	0.36
RMSSD (ms) (median, IQR)	46.22 (31.14–67.84)	39.47 (27.77–59.77)	<0.001

Data presented as mean±SD or median (IQR) for highly skewed data.
*Appropriate equality test based on normality.
BP, Blood pressure; BPM, beats per minute; CRTI, combat-related traumatic injury; HR, Heart rate; HRV, HR variability; RMSSD, root mean square of successive differences.

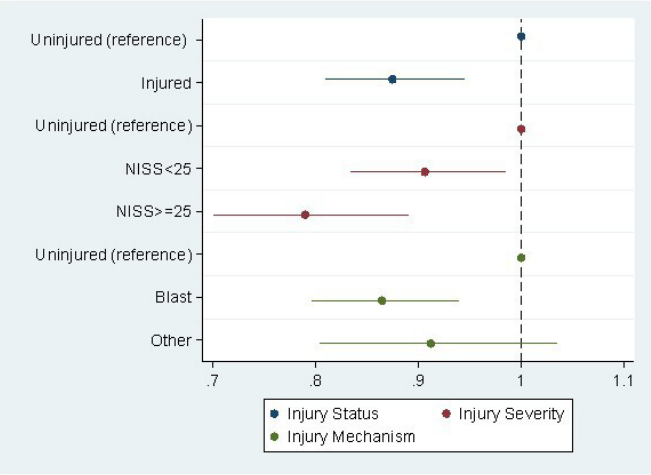

Figure 1 Geometric mean ratio (GMR) of the associations between root mean square of successive differences (RMSSD) and injury status, injury severity and injury mechanism. NISS, New Injury Severity Score.

linked to lower RMSSD and HRV, strengthening the plausible link between CRTI and its severity on lower HRV.

Another potential reason for lower HRV among the injured versus uninjured, in our study, could be the effects of CRTI on systemic inflammation.[21] In a previous publication from the ADVANCE study, it was shown that high-sensitivity C-reactive protein levels were significantly higher among injured versus uninjured participants and even higher in the most severely injured.[2] Finally, lower physical activity and greater relative abdominal obesity (visceral fat and abdominal waist circumference), following traumatic injury, may be other factors explaining the lower RMSSD among injured personnel.[2]

The significant association between injury severity and HRV_{UST} is a novel finding as there have been no previous studies to have examined the relationship between injury severity and HRV_{UST}. However, it has been previously reported that worsening injury severity was associated with greater high-frequency/low-frequency (HF/LF) power—among an injured population with acute traumatic injuries.[8] Hence, our findings cannot be directly compared owing to heterogeneity in scoring systems for injury severity (Injury Severity Score vs NISS), difference in time from injury, outcome measure (HF/LF vs RMSSD) and HRV type (short vs ultrashort term). Furthermore, during the acute postinjury period, there are considerable haemodynamic effects which are well known to affect HRV.[9] In our population, these effects would not be relevant as our cohort was on average 8 years post-injury with no open wounds.

Table 3 Multivariable linear regression analysis of RMSSD* with injury status, injury severity and injury mechanism

	Univariable	Model 1 (CRTI)		Model 2 (injury severity)		Model 3 (injury mechanism)	
	GMR	Adjusted GMR	P value	Adjusted GMR	P value	Adjusted GMR	P value
Injury status							
Uninjured	Ref			–	–	–	–
Injured	0.86 (0.79, 0.93)	0.87 (0.80, 0.94)	0.001	–	–	–	–
Injury severity (NISS 2008)							
Uninjured	Ref	–	–	Ref	–	–	–
NISS <25	0.89 (0.82, 0.97)	–	–	0.90 (0.83, 0.98)	0.02	–	–
NISS ≥25	0.79 (0.70, 0.90)	–	–	0.78 (0.69, 0.89)	0.000	–	–
Injury mechanism							
Uninjured	Ref	–	–	–	–	Ref	–
Blast	0.85 (0.78, 0.93)	–	–	–	–	0.86 (0.79, 0.93)	0.001
Other	0.89 (0.78, 1.01)	–	–	–	–	0.91 (0.80, 1.03)	0.15
Age at assessment	0.97 (0.96, 0.98)	0.96 (0.95, 0.97)	0.000	0.96 (0.95, 0.97)	0.000	0.96 (0.95, 0.97)	0.000
Rank							
Senior	Ref	Ref		Ref		Ref	
Middle	0.91 (0.79, 1.05)	0.95 (0.83, 1.08)	0.46	0.94 (0.82, 1.08)	0.43	0.95 (0.83,1.08)	0.46
Lower	0.94 (0.84, 1.07)	0.81 (0.71, 0.92)	0.002	0.81 (0.72, 0.92)	0.002	0.81 (0.71, 0.92)	0.002
Ethnicity							
Other	Ref	Ref		Ref		Ref	
White	1.05 (0.91, 1.20)	0.96 (0.84, 1.10)	0.62	0.97 (0.84, 1.11)	0.68	0.97 (0.84, 1.11)	0.67
Time from injury	0.97 (0.95, 0.99)	0.99 (0.97, 1.01)	0.87	0.99 (0.97, 1.01)	0.67	0.99 (0.97, 1.01)	0.87

Each model has been adjusted for age at assessment, rank, ethnicity and time from injury.
*Natural log of the root mean square of successive differences (RMSSD) was used in the regression analysis.
CRTI, combat-related traumatic injury; GMR, geometric mean ratio; NISS, New Injury Severity Score; Ref, reference category.

The independent relationship between blast as mechanism of injury and lower RMSSD in this study is an intriguing observation. Given the significant difference in injury severity between blast and other mechanisms observed in our study, the relatively lower HRV with blast might reflect the higher injury severity. However, injury severity could not be adjusted for with injury mechanism due to multicollinearity. The observed effect could also be explained by the systemic inflammatory response triggered by blast injury,[22] which in turn could affect HRV. Another explanation could be the effect of blast on endothelium function. In animal and human clinical studies, blast waves have been linked to endothelial disruption and associated dysfunction,[23] which itself is linked to lower HRV.[24] It is also plausible that the primary blast wave (vs other injury types) leads to traumatic brain injury and associated changes in brain stem activity[25] which was not directly quantified in this study.

The observed inverse relationship between age and HRV_{UST} (RMSSD) in our study supports current evidence. Increasing age has been consistently linked to a reduction in HRV.[26] However, it is difficult to directly compare RMSSD values obtained in our study with the age-corrected normative HRV_{UST} values. To our knowledge, there is only one study to date that has reported normative data for non-ECG-based HRV_{UST} and was conducted on 465 healthy Korean adults.[27] The meaningful comparison of our cohort with this population may not be appropriate owing to heterogeneity in terms of population characteristics and source of HRV data acquisition. This highlights a current research gap in normative data on non-ECG-based HRV_{UST} for both healthy adults and military populations.

Using ranks as a proxy for socioeconomic status, we found that servicemen at lower ranks had a lower HRV_{UST} than those at the higher rank across the whole cohort. This agrees with the current evidence on lower socioeconomic status and poor parasympathetic activity (reflecting depressed HRV), although based on short-term ECG-derived HRV in a non-military cohort.[28] The true confounding effect of socioeconomic class/rank on HRV following CRTI could be even greater than our results, given that the lowest ranks were the youngest (hence expected to have higher HRV) and yet had relatively lower HRV.

This is the first study to report on various aspects of CRTI (injury status, mechanism and severity) and HRV in military personnel and the first to examine non-acute injury. Our sample size is larger than most previous publications relating to traumatic injury and HRV with sample size <250.[29 30] Our inclusion of an uninjured comparison group of similar age, deployment and time from exposure to our injured group strengthens our findings. The blinding of the participant's injury/non-injury status at the time of HRV analysis is an additional strength that helped minimise reporting bias.

The findings in this study must be interpreted in the context of a few limitations. First, the current study represents a subset of 862/1144 participants from the full ADVANCE baseline cohort. This was due to the practical constraint of accessing the full arterial waveform data. Nevertheless, our population is very consistent with the demographics, injury severity and mechanism of the full ADVANCE cohort.[2] Second, we used the femoral arterial waveforms, rather than ECG data, to quantify the IBI and calculate $HRV_{UST.}$ The agreement between HRV measures obtained using IBI calculated using arterial waveforms (radial, brachial and digital) and surface ECGs has been well established.[12 13] However, the femoral arterial waveform represents the downstream physiological effect of ECG depolarisation and cardiac contraction. Owing to the short HRV recording period in this study, there is a greater vulnerability to the effects of ectopic beats and artefacts than that observed with longer HRV recordings. However, the signal quality was excellent with full signal disclose limiting this potential source of data error. There might also be some residual confounding as rank might not have been the best measure of socioeconomic status. However, it has been used as a suitable proxy for socioeconomic status in previous military research.[2 18] Moreover, the identified associations in this study do not equate to causation for which longitudinal studies are required. Lastly, it is likely that some mental and physical health factors might have contributed to the observed relationship as possible mediators. However, their exploration was beyond the scope of the current study. Therefore, a more in-depth exploration of the potential mediators along the CRTI-HRV causal pathway such as the influence of sleep, physical activity, quality of life and mental health is warranted to fully understand the effect of CRTI on HRV.

CONCLUSION

Injured UK personnel deployed to Afghanistan (2003–2014) demonstrate relative autonomic imbalance reflected in their higher resting HR and lower HRV_{UST} than that of a frequency-matched control group of uninjured servicemen exposed to the same operational environment. Worsening injury severity and blast injury were independently associated with lower HRV_{UST} after adjustment for covariates. Given the nature of this association, longitudinal studies are warranted to explore this relationship and the potential translational use of HRV—that is easy and quick to measure—in cardiovascular risk prediction among injured veterans.

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Patient and public involvement statement N/A

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the UK Ministry of Defence Research Ethics Committee (protocol number: 357/PPE/12). All participants provided full informed written consent. This study was conducted in compliance with the Declaration of Helsinki (1964). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Only the authorised authors (RM, CJB, ANB) had access to the data of this study. Given the sensitive nature of the participants, data have not been made widely available. Requests for data will be considered on a case-by-case basis

and subject to the UK Ministry of Defence clearance. More information can be found at: https://www.advancestudydmrc.org.uk/.

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