Headpulse Recovery in Recently Concussed Young Adult Athletes in Australian Football

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KEY POINTS

Question: In concussed athletes, are there characteristic temporal changes in cranial accelerometer derived headpulse biometric values in the month following sports-related concussion, and does local standard practice return-to-play alter these values?

Findings: In this prospective observational study of 43 concussed (with 44 total concussions) and 58 control athletes, 82% of subjects with clinically defined concussion were identified by analysis of 90-second noninvasive headpulse measurements compared to controls. More pronounced biometric abnormality was found in multiple subjects after return-to-play despite neurological symptom resolution.

Meaning: Findings suggest that serial measurement of the headpulse has diagnostic value for concussion and for concussion resolution but also reveals further abnormalities in concussed athletes returning to play within one month. These abnormalities may reflect subconcussive or other changes to the brain.

ABSTRACT

Importance: Concussion, a subset of mild traumatic brain injury, is common in sports. Current post-concussion return-to-play decisions are based in part on subjective symptoms. There is concern that returning to play too soon can cause long term neurological impairment or permanent brain injury.

Objective: To longitudinally characterize the 'headpulse', a cranial accelerometer derived concussion biometric generated by cardiac forces to the cranium, in a large series of subjects with sports-related concussion. We hypothesized that the headpulse would differ between concussed and control subjects. We explored the effect of unstructured physical activity on the headpulse in a subset of subjects.

Design: This was a prospective cohort study. Concussed and normal control athlete subjects were enrolled in two phases including a feasibility phase (A1) and a validation phase (A2). The A1 cohort was recruited between August 5, 2021, and September 10, 2021. The A2 cohort was recruited between May 5, 2022, and September 3, 2022. Controls were recruited from both A1 and A2 recruiting epochs.

Setting: Recruitment occurred within the Adelaide Football League which is the highest level of amateur Australian Rules Football in the state of South Australia, Australia. The first phase (A1) included 10 clubs with men's team participation. The second phase (A2) included 10 clubs with men's and women's team participation.

Participants: Subjects were adult male or female athletes. Athletes wear no padding or head protection and concussion is a frequent complication. Controls were required to be concussion free for more than 1 year by self-report. All subjects provided consent at the beginning of the season and were approached consecutively.

Interventions: Headpulse measurements were obtained using a lab-developed headset utilizing cranial accelerometry to transduce head forces (the headpulse) induced by cardiac contraction. An improved headset design minimized motion artifact in A2. Headset headpulse recording lasted 90 seconds each. Athletes were followed over one month with repeat recordings every 1-3 days. Subjects completed a Neurological Symptom Inventory (NSI) prior to each recording.

Main Outcomes and Measures: Headpulse waveform analysis involved frequency transformation then further evaluation using a prespecified algorithm devised in a prior study. Resulting calculated waveform pattern Z scores were used to compare subjects to controls. Headpulse determination of concussion was characterized as concussion subject Z scores that were 2 standard deviations from control subject Z scores. Outcomes included 1) sensitivity and timing of headpulse determination of concussion, 2) duration of concussion defined by symptom resolution compared to headpulse return to normal, and 3) exploration of presumed worsening headpulse signals in asymptomatic subjects.

Results: 100 subjects participated and had 723 recordings. There were 58 control subjects and 42 concussed subjects with 44 total concussions. The headpulse was tested in A1 then evaluated in A1 and A2 cohorts combined. The headpulse detected 82% of subjects who were diagnosed with concussion, with 50% identified by day 2 and 90% by day 14 following concussion. Compared to symptom resolution by NSI scores, the headpulse resolution lasted 12 days longer on average. Exacerbations in headpulse abnormality occurred more frequently in those who returned-to-play or engaged in unstructured or unsupervised physical activity.

Conclusion and Relevance: Findings suggest that serial measurement of the headpulse has diagnostic value for concussion and for concussion resolution but also reveals potentially subconcussive changes in injured athletes returning to play within 1 month. Since the headpulse is objective, its use may have a role in supporting return-to-play clinical decision making.

Trial Registration: ClinicalTrials.gov (NCT05769296, NCT05771051), Australian New Zealand Clinical Trials Registry ACTRN12621001707853.

INTRODUCTION

Traumatic brain injury (TBI) causes significant morbidity and mortality with an annual global incidence exceeding 60 million.[1] One third of injuries are sports related with predilection for young adults.[2] The vast majority of TBI is technically classified as 'mild' using current diagnostic criteria and concussion is a subset of mild TBI. Concussion symptoms can be debilitating and include headache, vestibular impairment, visual changes, cognitive symptoms, mood changes, and sleep disturbance.[3,4] A second concussion during recovery can be neurologically deleterious and in rare cases fatal (e.g., 'second impact syndrome').[5] More commonly, greater than 50% of concussed individuals have persisting symptoms one year from injury.[6] Repetitive concussive or asymptomatic subconcussive events are also associated with delayed onset neurobehavioral impairment and subsequent neuropathological findings of chronic traumatic encephalopathy (CTE) and other neurodegenerative conditions.[7-12] Risk factors for repetitive head injury and CTE are well described in the literature and include collision sports. To mitigate these risks, most organized sports teams utilize concussion protocols which prohibit return to play (RTP) before recovery but this is also clinically determined. Objective identification of concussive injury, asymptomatic subconcussive injury, and definitive recovery is critical to mitigate both short- and long-term impairment.

There are no objective metrics that confirm sports-related concussion (SRC) and recovery. The US National Academies of Science, Engineering, and Medicine recently published a detailed report urging improved injury characterization and classification[13] in part due to biomarker development. In our study, we present a potential digital biomarker derived from cranial accelerometry (CA) which draws on principles of ballistocardiography first recognized in the 19th century. Ballistocardiogtraphy is a technique that measures whole body forces produced by cardiac contraction.[14-16] These forces can be transduced on the head using highly sensitive accelerometers. We call the related waveform the 'headpulse'. We previously showed that frequency domain analysis of the headpulse can support a diagnosis of concussion and its recovery.[17] We have also shown headpulse abnormalities in moderate to severe TBI[18], large vessel stroke[19,20], cerebral vasospasm[21], and cardiac arrest.[22] In the current study, we evaluated a longitudinal cohort of concussed and control athletes to investigate the time course of headpulse signal change (Australian University of california San francisco concussion Study In athlEtes, AUSSIE-1, A1). Our model was then validated in a second cohort (AUSSIE-2, A2).

METHODS

This was a prospective feasibility (A1) then validation (A2) study involving athletes from the Adelaide Football League which is the highest level of amateur Australian Football in Adelaide, South Australia. A total of 762 athletes provided written consent at the beginning of the season. The study was approved by the Human Research Ethics Committee of Bellberry Limited, a national, private not-for-profit organization which provides scientific and ethical review of human research studies in Australia (HREC protocol number 2021-09-1104).[23] The study was performed in two phases to confirm feasibility and refine methodology required to obtain reliable headpulse data (A1) in order to validate the study (A2); A2 additionally included female athletes and explored the influence of physical activity on headpulse patterns. Both trials have been registered at ClinicalTrials.gov (NCT05769296, NCT05771051), and Australian New Zealand Clinical Trials Registry (ACTRN12621001707853).

Subjects

Subjects were adult male or female athletes. A1 included 10 clubs with men's team participation. A2 included 10 clubs with men's and women's team participation. The A1 cohort was recruited between August 5, 2021, and September 10, 2021. The A2 cohort was recruited between May 5, 2022, and September 3, 2022. Controls were recruited during the same periods and were required to be concussion free for more than one year by self-report.

Procedures

The study was designed to align with local procedures including approach to concussion diagnosis and return-to-play decisions.[14] Research coordinators attended games and were alerted to players with new concussion. An attempt was made to record from concussed athletes as soon as possible following injury. All but one initial recording were conducted within one hour of concussion. Coordinators traveled to subjects' home every 1-3 days for a month following injury to obtain additional recordings. The A2 cohort was encouraged to wear a wristband accelerometer after injury to document physical activity (FitBit, Inspire 2. Alphabet, San Francisco, USA).

Headpulse Recordings: Recordings were obtained from a battery-powered noninvasive headset device comprised of highly sensitive accelerometers attached to a headband. The headband was placed on the subject's head in the coronal plane (Figure S2) and facilitated recording of the headpulse which is comprised of forces on the head produced by the cardiac contraction in the 10-15 milli-g (g, gravitational force unit) range. In A1, bilateral triaxial accelerometers were placed anterior to the ear over the temporal bone. In A2, a commercial device (MindRhythm, Inc, Cupertino, CA) with a unilateral triaxial accelerometer was used. Devices transduced the electrocardiogram (ECG) using a standard 3-lead system to provide heartrate information. Devices also connected to an iPhone using Bluetooth and custom software. Recordings lasted 180 seconds in A1 cohort, and 90 seconds in A2, and were obtained in the seated position while the subject was asked to hold their head still and not speak or chew. Gross body motion overpowers the headpulse and excessive body movement degraded some recordings in A1 so the A2 headset (MindSafe, MindRhythm, Inc, Cupertino, CA) was designed to provide feedback to participants when motion was detected. This led to fewer excluded recordings. Subjects completed an adapted Neurobehavioral Symptom Inventory (NSI)[24,25] (Supplemental materials, Section III) on the iPhone with each recording. Data was offloaded via micro-SD card. Athletes and study personnel were blinded to headpulse analyses and headpulse did not impact existing RTP protocols.

Activity Tracking: Some A2 subjects consented to wristband accelerometry (FitBit Inspire 2). 'Fairly active' and 'very active' number of minutes served as proxy for physical activity.

Data Analysis: Data files were submitted to custom software (MATLAB, MathWorks, Natick, MA) to analyze frequency data as previously described.[17] Time domain accelerometry signals from the right-sided accelerometer for 45 heart beats were converted to the frequency domain using Fourier transformation. The average heartrate during the recording was derived from R-wave analysis of the ECG. This average heartrate provided the fundamental and harmonics of the heartrate, and the frequency transform was sampled at the fundamental and successive harmonics 2-9. Factors R1 and R2 were calculated as the ratio of the mean of the 5th and 6th harmonics by the mean of the harmonics 1-3 (R1) and the mean of the 7th and 8th harmonic divided by the mean of harmonics 1-3 (R2) (Figure S1).[17] R1 and R2 values for controls were calculated and subject R1 and R2 values were analyzed as Z scores above or below the mean control values. Higher R1 and R2 Z scores represent higher frequency shift of the headpulse following TBI.[4,17,18] We defined any recording exceeding two standard deviations (SD) of controls to be significant, and the earliest value to exceed this threshold was defined as biometric (or headpulse) onset time of abnormality. R1 and R2 values and corresponding NSI scores were plotted over time. A Kaplan-Meier curve representing freedom from biometric abnormality was calculated to illustrate diagnostic sensitivity compared to controls and to illustrate latency from concussive event to first abnormal device recording. To document recovery from concussion, the duration from biometric concussion onset to a zero NSI score was tabulated; if the subject did not return to a zero NSI score during their recording period the subject was considered not clinically recovered. For subjects who did not have a threshold biometric onset time, the biometric duration was defined as zero. For subjects with threshold biometric onset, the recovery period was defined as duration from concussion to time that all ratios fell under one SD from the mean. The choice of one SD was based on the observation that R1 and R2 ratios fell over time in a characteristic fashion, allowing for objective quantization of biometric defined concussion parameters.

RESULTS

We found characteristic headpulse changes after acute injury and marked asymptomatic headpulse abnormalities in those with RTP. Measurement, analysis, and compilation of controls are detailed in the online supplement. Study groups are shown in Figure 1. Of 762 athlete volunteers, a total of 100 subjects had headpulse measurements including control (n = 58) and concussed (n = 43) subjects; one subject enrolled as a control was later concussed (so counted twice) and one concussed subject in A2 sustained two concussions separated by more than 1 month for a total of 44 concussions. Table 1 shows subject demographics. Subjects had similar years of education. Female athletes had fewer self-reported prior concussions than males. In A2, male control and concussed athletes had historically played more games than female athletes (proxy for concussion exposure) but there were no significant differences of games played between control and concussion subjects within genders. Among concussed subjects, 4 (10%) had loss of consciousness (LOC), 16 (39%) had alteration in consciousness, and 7 (17%) had transient post-traumatic amnesia (PTA) at time of injury. Concussion was diagnosed by a physician in 7 (17%), team staff member in 25 (61%), the subject in 8 (20%), and 1 was unknown (2.4%). The diagnosis of concussion followed AFL guidelines.[26] No subject sustained a concussion within the month following injury although many returned to play within this timeframe.

In A1, 40 of 184 (22%) of recordings were motion degraded yielding 144 recordings. In the A2 validation cohort we used an improved device that provided feedback to the research coordinator of ongoing excessive body motion (MindSafe device, provided by MindRhythm, Inc, Cupertino, CA). This resulted in fewer rejected recordings due to excess body motion (24/276 = 8.7%).

All subjects provided headpulse recordings over one month following injury. Data were used to explore the time course of R1 and R2 values. Figure 2A shows data from a concussed female athlete who underwent 16 recordings over the following month. She was most symptomatic on day 0, felt better the next day, developed symptom exacerbation, then had few symptoms for the remainder of the month. Her R1 and R2 values rise after concussion but lag symptom severity by 1-2 days. This lag was characteristic of most subjects and is described further below. As another example, recordings from a concussed male athlete are shown in Figure 2B. This subject had minor symptoms on day 0 then reported no symptoms for the remainder of the month. However, R1 and R2 became abnormal 3 days following concussion and continued to oscillate. He was released to play per protocol (release to play after day 12 if neurologically asymptomatic is common in AFL players); despite having no symptoms he developed even higher elevations in R1 and R2, suggesting that RTP impacted headpulse values.

To investigate the influence of physical activity on the headpulse following concussion, in A2 we provided a commercial wrist-mounted accelerometer (Fitbit) to document gross physical activity as soon after concussion as possible. Figure 3 shows an example of this analysis. A male subject developed marked R1 and R2 increases despite asymptomatic status, with increases following physical activity unrelated to play. Although he did not RTP until 13 days following concussion, he vigorously exercised and continued to feel well (physical activity in lowest trace as defined by wrist accelerometer device). This subject demonstrated even greater subsequent increases in R1 and R2 values after RTP. Six subjects attempted to wear the Fitbit in A2, and 4 used Fitbit for more than 1 day. Of these 4, all had R1/R2 increases above concussion threshold after Fitbit-determined physical activity by 2,3, 7, and 8 days.

Combining A1 and A2 cohorts, later elevations in R1/R2 occurred mostly in subjects who returned to play (Figure 4). Figure 4A shows the average NSI score and average R1 values for all subjects by day since concussion. In those who returned to play (Figure 4B), NSI values returned to zero and mostly stayed low for the rest of the month. Later rises in R1/R2 occurred with values reaching the highest seen in those with RTP. In comparison, those without RTP remained symptomatic longer (Figure 4C) and had lower R1/R2 values on average.

To explore headpulse sensitivity for concussion and recovery detection, all concussed subjects (44 total concussions) with more than 2 noise-free recordings during the first week were examined; 7 declined participation following their first recording and 5 had recordings degraded by noise, leaving 32 concussions for this analysis (12 from A1 and 20 from A2). Using biometric abnormality threshold of 2 SDs above the mean of control subject R1 and R2 values, in A1, 10/12 (83%) were classified as concussed. Combining A1 and A2, 26/32 (81%) of all concussed athletes had one or more readings above this threshold (Figure 5A), validating sensitivity. Overall, combining the 2 cohorts, CA detected 9.4% of concussions on day 0, 50% by day 2, and 90% by day 14.

Biometric abnormality duration was substantially longer than clinical symptom duration which was determined as time from concussion onset until NSI achieved a value of zero (of 32 subjects, 26 had NSI values returning to normal by the last recording). Figure 5B shows that within 30 days, 81% of athletes scored 0 on NSI, with 50% achieving an asymptomatic state by day 7. For biometric abnormality duration, we considered subjects who had at least 1 recording 2 SD above the normal mean with return to below 1 SD of the mean at or prior to the last recording (N= 15). Compared to clinical symptom resolution, only 53% of athletes demonstrated biometric resolution by day 30 with 50% achieving this by day 19, 12 days later than NSI improvement. Since LOC and PTA during index event may represent more severe concussive injury[27], we specifically reviewed subjects with LOC, PTA, or both to query pattern aberrations. No differences in maximum biometric value were seen for those with LOC, PTA, or both compared to those without either sign or symptom ($p > 0.24$, pooled t-test).

DISCUSSION

To our knowledge, this is the largest series of longitudinal concussion cranial accelerometry derived headpulse measurements, expanding on prior findings.[17] While controls were evaluated in Auerbach *et al* (n = 74) and a recent case series (n = 5)[28], female subjects were not included. In the present study, we demonstrated feasibility of data collection and analysis (A1) then validated findings in A2 which additionally included female athletes. Device sensitivity was 82%. Injury-related headpulse R1 and R2 values met our prespecified threshold for concussion (i.e., a ‘positive’ biometric) but there was a 1-3 day lag and biometric positivity was not always concordant with symptom endorsement. After concussed athletes returned to play (15 subjects) or other activities (Fitbit, 4 subjects), R1 and R2 values rose or remained elevated despite low or no symptoms, suggesting that asymptomatic athletes who tolerate physical activity experience intracranial changes after RTP. These changes may represent injurious sequelae like subconcussive injury.

Previously, Auerbach *et al* demonstrated a similar R1 and R2 concussion threshold in 13 concussed and 69 normal control high school US football athletes with 77% sensitivity and 87% specificity. Case examination also revealed delayed headpulse concussion designation with gradual return to normal patterns, but after symptom resolution. We used the same algorithm and replicated these delays in a larger population.

The current concussion biomarker landscape includes candidate metrics of differing modalities. Among blood-based metrics, glial fibrillary acidic protein (GFAP) and ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) are approved by the US Food and Drug Administration (FDA) for use in determining need for head computed tomography (CT) in emergency department settings.[29-31] GFAP and UCH-L1 are also elevated in SRC and may have prognostic value.[27] McCrea and colleagues found that GFAP and UCH-L1 levels were higher still in concussed subjects with injury-related LOC and PTA; GFAP and UCH-L1 levels were highest acutely while neurofilament light chain (NF-L) levels increased over days in those with LOC and PTA.[27] Candidate neuroimaging metrics are not yet validated for routine clinical practice and include diffusion tensor imaging, functional imaging such as resting state or task-based network status, and markers of cerebrovascular reactivity.[32] In our study, delayed headpulse abnormalities with further rise of R1 and R2 values following early unstructured activity align with other markers that demonstrate a time-dependent course.

The etiology of headpulse harmonic shifts to higher R1 and R2 values is not yet known. We also cannot determine directionality of changes; it is unclear if shifts reflect evolving concussive pathophysiology or compensatory changes. Concussive injury triggers overlapping, interrelated events including cell membrane associated ionic shifts, neurotransmitter release, cerebral blood flow and vascular reactivity changes, and metabolic crisis.[12] Speculative causes of headpulse signal changes in concussion therefore include alterations in brain parenchymal mechanical resonance (i.e., the brain is stiffer) additionally modulated by cardiovascular or neurovascular response. For the few subjects with Fitbit activity quantification, etiology of R1 and R2 elevations following unstructured activity is not yet known. Care must be taken to interpret this and other RTP R1/R2 rises given demonstrated efficacy of *structured* exercise as a treatment for concussion in sports and military settings[33-38]; a potentially relevant finding in our study is the persistence of symptoms for those with delayed RTP or low/no activity levels.

Our study has several strengths. Subjects and research coordinators were blinded to analyses. Subjects included female athletes, an understudied concussion population. Longitudinal recordings allowed us to examine the cadence of headpulse pattern changes. The NSI served as a proxy for ongoing symptom burden and was collected with each headpulse recording, revealing the headpulse/symptom mismatch. The algorithm used to identify R1, R2, and the related concussion threshold was applied.[17] Finally, the study embedded experimental procedures with local approaches to RTP without headpulse influence, allowing for observations that are likely generalizable within standard practices in amateur or recreational settings as some subjects returned to play before the otherwise mandatory 12 day abstinence period in Australian Rules Football. The latter serves as a limitation, however, since study points of entry and exit were not standardized such as with uniform diagnostics or pre- or post-season testing. Another limitation is that 7 concussed subjects provided only the first recording before withdrawing. In addition, 72 of 723 recordings were motion degraded but this prompted a study procedure change in A2 in which the newer generation headpulse device software notified the recording research coordinator of excessive motion. Finally, history of concussion was elicited by self-report though this identified a high prevalence of prior concussion. Despite these limitations, cranial accelerometry offers a simple, noninvasive, easy to use method for headpulse determination. We have shown that headpulse patterns change in a characteristic manner in SRC, and similar to other candidate biomarkers described above, the headpulse remains altered beyond the point of symptom resolution.

Concussion and concussion recovery remain clinical diagnoses. Biomarkers serve to support and not replace clinical diagnosis but can enhance injury characterization. Tracking the headpulse following concussive injury may objectively aid personalized RTP decisions which are currently anchored on symptom burden or exacerbation. Minimizing risk of subsequent concussive and subconcussive events is critical to prevent long term impairment while preserving the spirit and benefits of sport. Next steps include determining feasibility of headpulse device self-administration by a concussed individual, broader activity tracking, and enhanced injury and recovery characterization via cognitive and clinical assessments.[4]

Acknowledgements

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TABLE AND FIGURE CAPTIONS

Table 1: Demographics

Subtext: *Median (interquartile range)

Figure 1: Standards for Reporting of Diagnostic Accuracy Studies (STARD) diagram of consented, enrolled, and analyzed subjects. An enrolled subject had at least 1 headpulse recording. One subject enrolled as a control was later concussed (so counted twice) and one concussed subject in the A2 cohort sustained two concussions separated by more than 1 month. Recordings that contained excessive body motion or had poor quality ECG recordings were excluded. For the analysis of onset and recovery which required 2 or more recordings in the first week following injury, 12 subjects were excluded (3 because of poor quality recording and 9 who withdrew after the first recording) resulting in 32 subjects for this detailed analysis. Per subject recordings are reported as median (interquartile range).

Figure 2: (A) Female subject sustained a concussion during an Australian Football game. The top trace is her NSI score time-locked to each headpulse recording over the course of a month. The vertical dashed orange line is the time of concussion and the blue line depicts return to play. The bottom three panels are the vertical, anterior-posterior, and lateral accelerometry headpulse recordings obtained while she was resting in the seated position. R1 and R2 values are shown for each recording. Ordinate values are Z-scores of R1 and R2 values compared to the mean of controls; a dashed line at 2 indicates 2-standard deviations above control means. The first recording crossing the 2-SD line in any axis is defined as biometric onset time of concussion. As was typical of both cohorts, the R1 and R2 values become abnormal on day 2, return to normal on day 5-7 then rise and fall again in an 'M-shaped' fashion. This subject was sedentary until she returned to play. She experienced a later rise in R1/R2 values on day 13 then returned to normal for the remainder of the month. This is an example where the biometric signal parallels the NSI. **(B) 21-year-old male with 2 prior concussions was knocked to the ground, stood up and was ataxic then fell.** His NSI score reveals minimal self-reported symptoms, and his cranial accelerometry recordings show significant rise/fall/rise/fall pattern as identified in the A1 cohort. Having no concussion symptoms, he was returned to play on day 13 and did not have return of symptoms. Despite being asymptomatic his biometric later rose above 2 standard deviations and did not return to normal. This is an example where the biometric signal is independent of the NSI.

Figure 3: A 19-year-old male subject with no known prior concussions sustained a concussion during an Australian Football game. Figure layout is defined in Figure 2. In addition to the headpulse recordings, the subject wore a wrist-mounted accelerometer. Activity is defined as 'fairly active' and 'very active' by the device manufacturer (FitBit, Alphabet, San Francisco, CA). This device documented a significant amount of physical activity in the days preceding the rise at day 10 before he returned to play on day 14 despite being advised to remain sedentary per local guidance. The subject discontinued the exercise tracking device on day 14. Four other subjects had good quality wrist-accelerometry and all 4 had worsening of the biometric following initiation of exercise.

Figure 4: (A) Average NSI and biometric values (R1 vertical axis) for A1 and A2 cohorts having more than 1 recording following concussion (N=32). Top row of x-axis labels are days since concussion; lower row is number of subjects contributing to the

average. The average NSI declines to zero on day 14, then later rises. The average biometric value has an M-shaped time trajectory over the first 7 days and again rises on day 7 and 14 after 5, then 6 players returned to play (black arrows; RTP sooner than day 12 was not recommended by local protocols; 2 others return on day 20 and 2 more on day 27). **(B) Analysis comparing those who returned to play and those who did not (C).** The NSI scores were lower in those who returned to play showing that team leadership kept players with continued concussion symptoms away from play but there was a discordance with biometric values.

Figure 5: (A) Time curve of concussion free status as detected by R1 and R2 values in the A1 and A2 cohorts who had more than one recording (N=32). Overall, 81% of subjects with the clinical diagnosis of concussion had significant increases in R1 or R2 in the first 30 days. On the day of concussion (day 0) 9.4% were abnormal, 50% were abnormal by day 2 (upper dashed line) and 90% were abnormal by day 14 (lower dashed line). Green dots indicate censoring of subjects. (B) Comparison of concussion recovery by NSI returning to zero (blue line) and return of biometric ratios below one standard deviation from the mean of normal (gold line). Green filled circles indicate censoring. By 30 days, 81% of subjects had returned to a zero NSI score, compared to 53% of subjects returning to normal biometric values. By day 7, 50% of subjects had a zero NSI score (upper dashed line), compared to day 19 for those defined by biometric ratios (lower dashed line) suggesting that biometric abnormalities resolve around 12 days following traditional definitions of concussion recovery.

	Aussie-1 Control	Aussie-1 Concussion	Aussie-2 Control	Aussie-2 Concussion
Female: Male (N)	0:18	0:15	25:17	9:19
Age, female*			21 (19.5-21.5)	28 (20.5-30.5)
Age, Male*	22 (19-27.3)	21 (19-22)	26 (22.5-28.5)	21 (19-22)
Education, female (yr)			14 (12-15)	16 (12.5-17.5)
Education, male (yr)	14 (12-12)	15 (12-15)	17 (13.5-17.5)	12 (12-15)
Prior concussion, female (%)			32.0%	44.4%
Number concussions, female*			1 (1-0)	6 (1.3-10)
Latency of last concussion, female (yr)			5 (2-11)	5
Prior concussion, male (%)	61.1%	73.3%	41.2%	73.7%
Prior concussions, male*	2 (1-4)	2 (2-4)	2 (1-3)	2.5 (2-4)
Latency of last concussion, male (yr)*	3.5 (1.9-7.5)	3.5 (2.6-5.3)	6.5 (4-10)	3 (1.5-6)

Figure 1

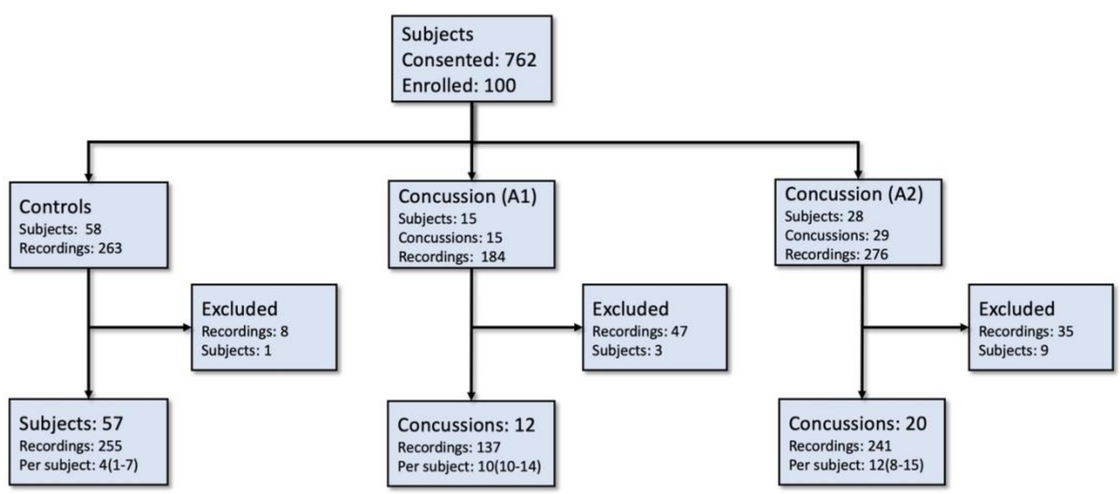
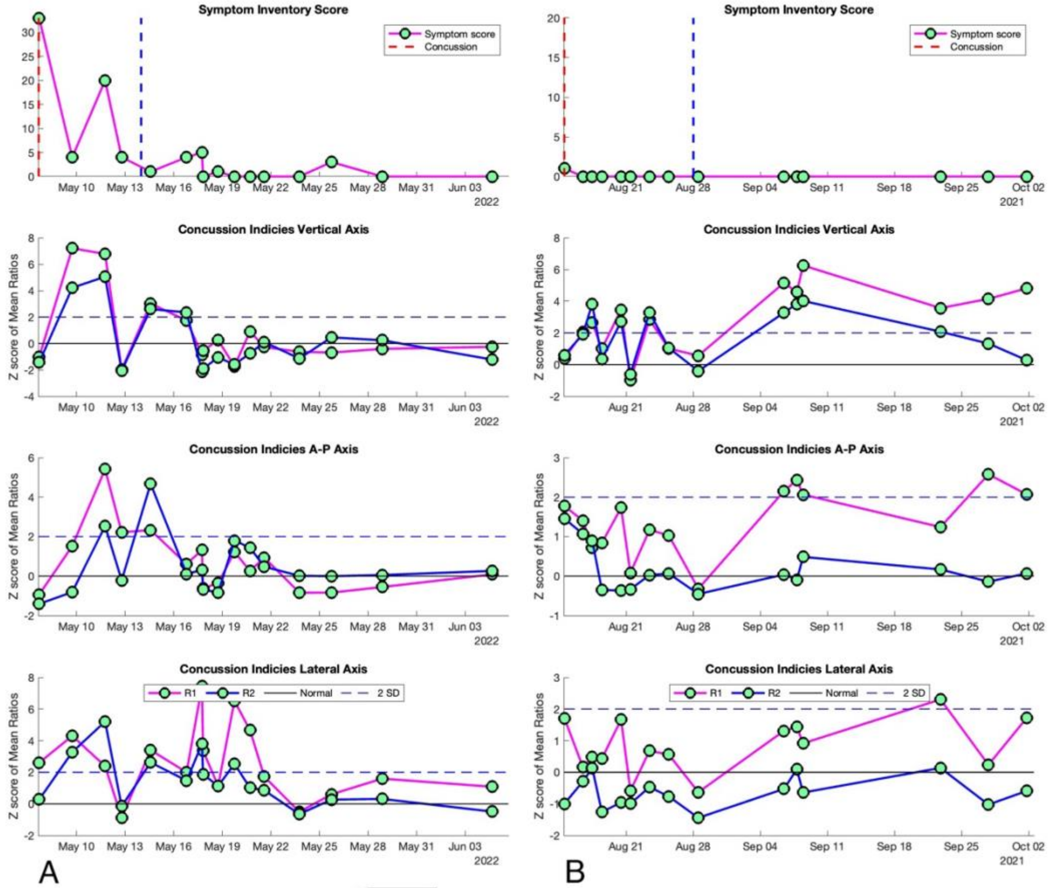
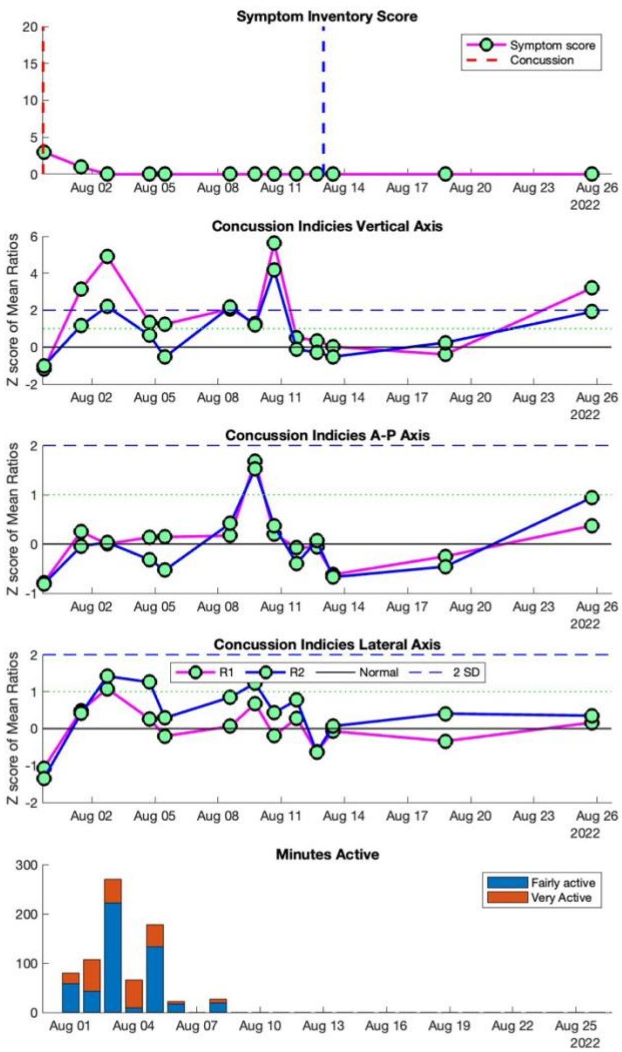


Figure 2



Symptom Inventory Score
Symptom score
Concussion
Concussion Indicies Vertical Axis
Concussion Indicies A-P Axis
Concussion Indicies Lateral Axis
Z score of Mean Ratios
R1
R2
Normal
2 SD
May 10
May 13
May 16
May 19
May 22
May 25
May 28
May 31
Jun 03
2022
Aug 21
Aug 28
Sep 04
Sep 11
Sep 18
Sep 25
Oct 02
2021
A
B

Figure 3



Symptom Inventory Score
Symptom score
Concussion
20
15
10
5
0
Aug 02
Aug 05
Aug 08
Aug 11
Aug 14
Aug 17
Aug 20
Aug 23
Aug 26
2022
Concussion Indicies Vertical Axis
Z score of Mean Ratios
Concussion Indicies A-P Axis
Concussion Indicies Lateral Axis
R1
R2
Normal
2 SD
Minutes Active
Fairly active
Very Active
300
200
100
Aug 01
Aug 04
Aug 07
Aug 10
Aug 13
Aug 16
Aug 19
Aug 22
Aug 25

Figure 4

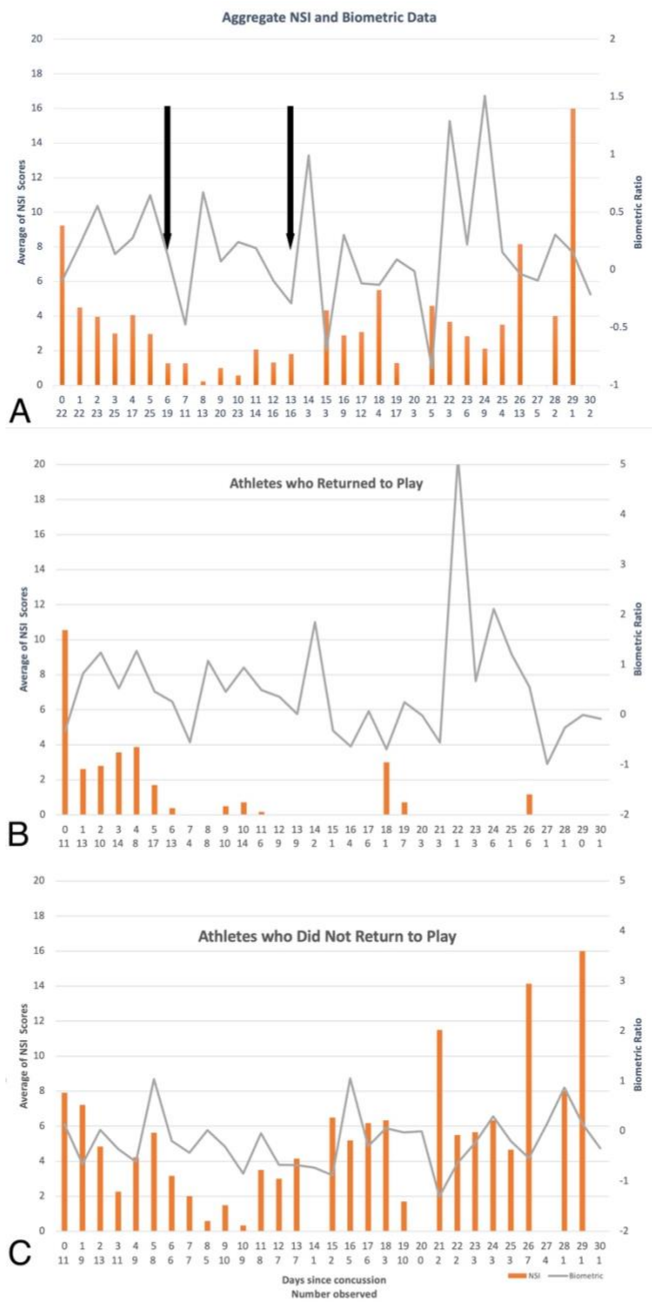
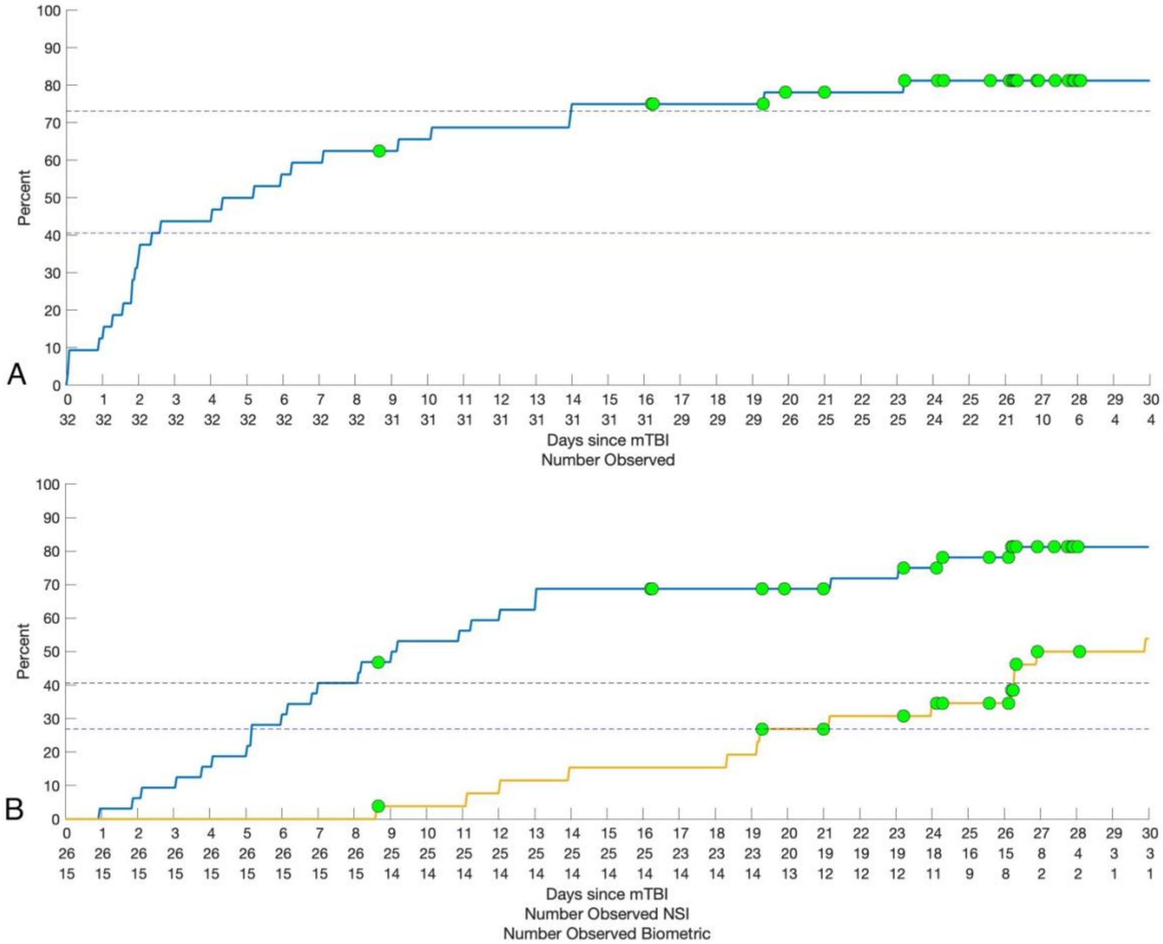

Aggregate NSI and Biometric Data
Average of NSI Scores
Biometric Ratio
A
Athletes who Returned to Play
B
Athletes who Did Not Return to Play
C
Days since concussion
Number observed
NSI
Biometric

Figure 5


A
Percent
100
90
80
70
60
50
40
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10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
32 32 32 32 32 32 32 32 32 31 31 31 31 31 31 31 31 29 29 29 26 25 25 25 24 22 21 10 6 4 4
Days since mTBI
Number Observed
B
Percent
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
26 26 26 26 26 26 26 26 26 25 25 25 25 25 25 25 25 23 23 23 20 19 19 19 18 16 15 8 4 3 3
15 15 15 15 15 15 15 15 15 14 14 14 14 14 14 14 14 14 14 14 13 12 12 12 11 9 8 2 2 1 1
Days since mTBI
Number Observed NSI
Number Observed Biometric

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