Standard Clinical Examination is not Prognostic of Impending Cognitive Fatigue

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Disclosures

We have no actual or potential conflicts of interest to disclose in relation to this presentation.

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Department of Defense — USAF: 711th Human Performance Wing *"Establishing biomarkers of post- sortie cognitive fatigue"*

Human Research Protections/IRB Statement
The study protocol was approved by the Naval Medical Research Unit Dayton Institutional Review Board in compliance with all applicable federal regulations governing the protection of human subjects. A reliant agreement was arranged with the Case Western Reserve University Institutional Review Board.

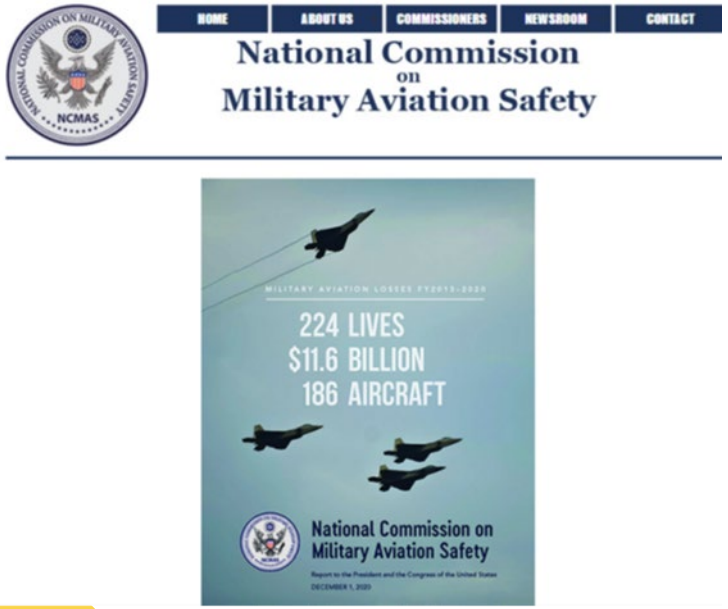
All photographs and images are courtesy of the Decker lab

Study Impetus

May 2019: USAF Safety Officer asked us to investigate causes of cognitive fatigue reported by instructor pilots who fly multiple flights/day training student pilots

Cognitive Fatigue

A constant threat to human performance and aviator safety, is the “likely cause of the next mishap” National Commission on Military Aviation Safety: Report to the President and Congress



Preventing that mishap is hampered by an absence of quantitative physiologic biomarkers that correspond to and predict increasing levels of fatigue.

Cody, R.A., Healing, R.F., Donnelly, S.C., Johns, R.E., Geren, P., Kern, D.R., and Hagin, J.W. (2020). National Commission on Military Aviation Safety. Report to the President and the Congress of the United States, 1-143.

Distinguishing Fatigue from Sleepiness

- **Fatigue** can be defined as:
  - Performance fatiguability, which is declining performance over a discrete period
  - Perceived fatiguability, which are changes in the (bodily) sensations that influence the "soundness" of the performer

- **Sleepiness** can be defined as:
  - The difficulty in maintaining a desired level of wakefulness. It is frequently viewed by the general population as a common experience and a predictable consequence of insufficient sleep.

Enoka R, Duchateau J. Translating Fatigue to Human Performance, Medicine & Science in Sports & Exercise: November 2016 - Volume 48 - Issue 11 - p 2228-2238.

Young TB. Epidemiology of daytime sleepiness: definitions, symptomatology, and prevalence. J Clin Psychiatry. 2004;65 Suppl 16:12-6.

Our Question

- Can current or impending fatigue be readily detected through routine clinical measurements?

The Study Cohort

- Study participants were T-6A Texan II Instructor Pilots who were scheduled to fly at least two flights during the week of data collection.
- Data were collected on three separate days across the week-long flying schedule.

What We Measured

Physical Assessment
- Brief health history
- Height
- Weight
- Vital signs

Spirometry
-Pulmonary Function

Venous Phlebotomy
- Blood chemistry
- Serum analysis

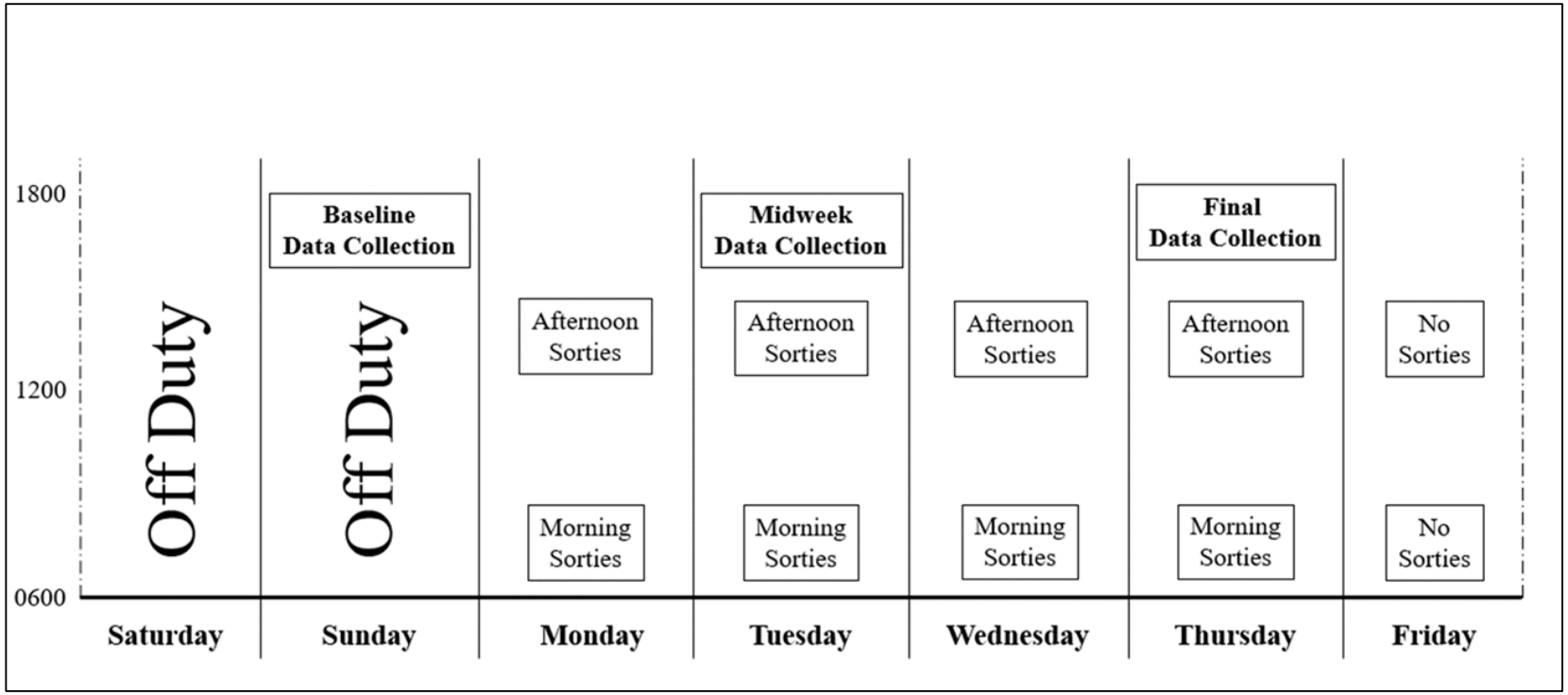
Arrival Post-Sortie

Participant Departure

MFI
- General Fatigue
- Physical Fatigue
- Mental Fatigue
- Reduced Motivation
- Reduced Activity

Urine Assessment
- Specific gravity

When We Measured It



Sample Demographics (N=22)

Sex	**Age (years)** M ± SD *(Range)*	**BMI (kg/m^2)** M ± SD *(Range)*
Males n = 20	37.95 ± 4.73 *(29-47)*	26.63 ± 3.15 *(21.92-32.63)*
Females n = 2	41.00 ± 0.00 *(41-41)*	24.38 ± 1.61 *(23.24-25.52)*
***p*-value**	0.21	0.36

No age or BMI differences between males and females

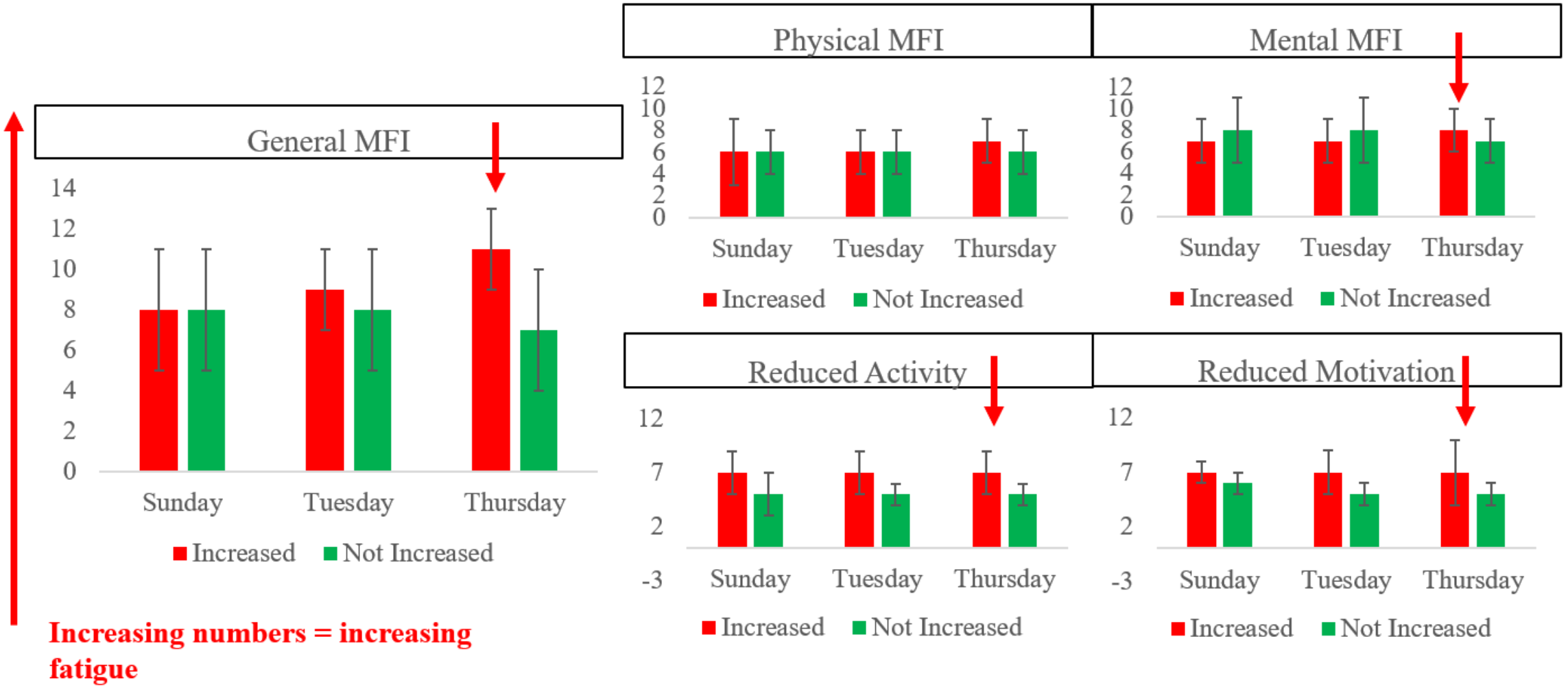
(p-values from Wilcoxon rank sum test)

Fatigue Measurement

- The **Multidimensional Fatigue Inventory (MFI)** was used to assess five dimensions of fatigue:
  - Physical Fatigue
  - Mental Fatigue
  - General Fatigue
  - Reduced Activity
  - Reduced Motivation
- Scores range from 4 (no fatigue) to 20 (incapacitated by fatigue); higher scores correspond worsening levels
  - Third-year medical students ~7
  - Scores >10 have been associated with a state of being “unwell”
  - Chronic Fatigue Syndrome ~13

Lin, J.M., Brimmer, D.J., Maloney, E.M., Nyarko, E., Belue, R., and Reeves, W.C. (2009). Further validation of the Multidimensional Fatigue Inventory in a US adult population sample. Popul. Health. Metr. 7, 18. doi: 10.1186/1478-7954-7-18

Multidimensional Fatigue Inventory (MFI) results

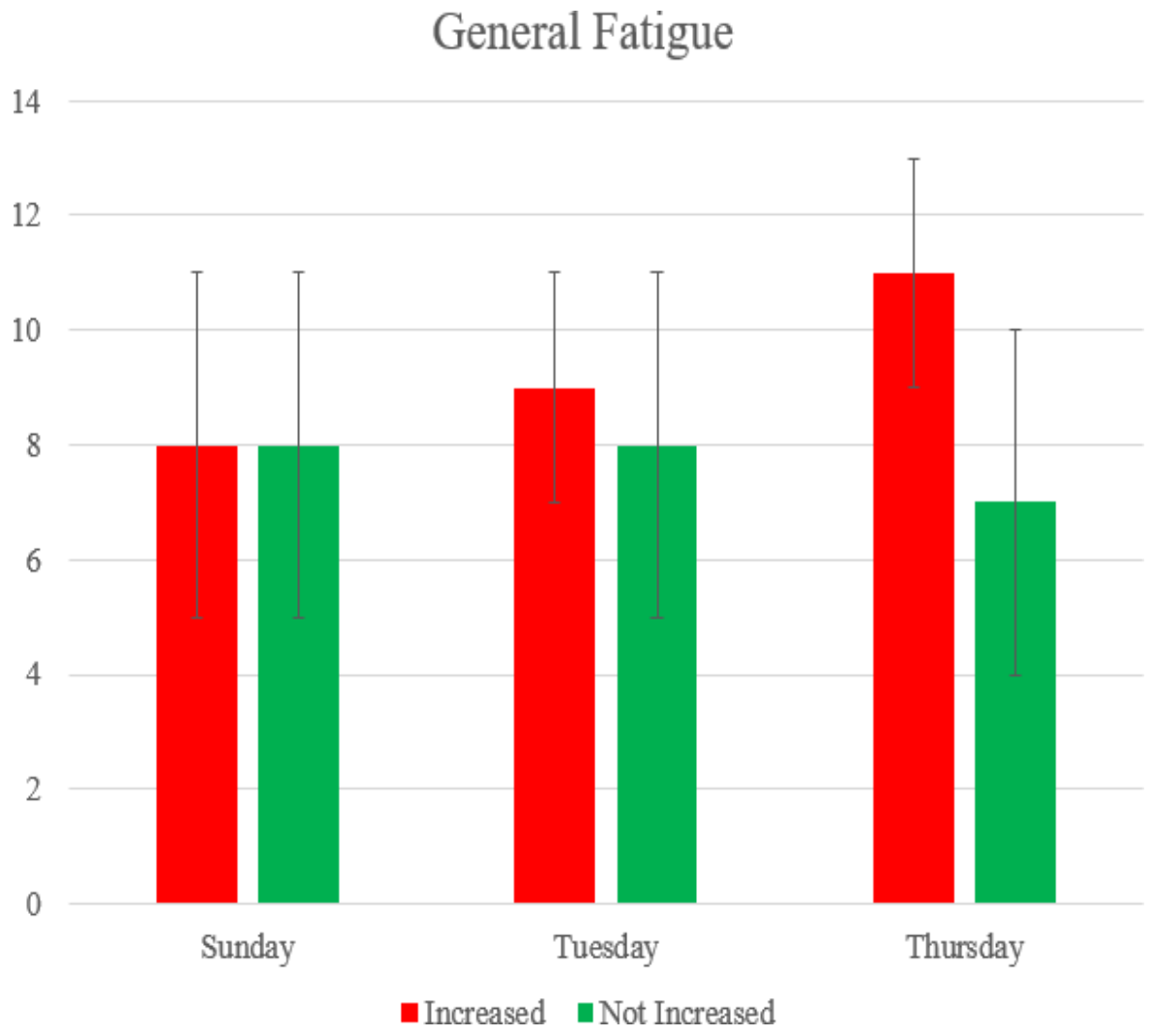


We found that all IPs felt about the same on a Sunday afternoon (baseline). By the end of the week, **13 out of 22 IPs** reported significantly more fatigue (red bars).

Self-Reported Fatigue

Participants were categorized into two groups:

- Thursday (final) General Fatigue score higher than Sunday (baseline)
  - n = 13
- Thursday (final) General Fatigue score **not** higher than Sunday (baseline)
  - n = 9



Fatigue Distribution

Those 13 also showed increases in Mental Fatigue, Reduced Activity, and Reduced Motivation

MFI Scores	Increased n=13 M ± S.D (range)	Not Increased n=9 M ± S.D (range)	p-value
Physical	7.15 ± 2.08 (4-10)	5.78 ± 1.86 (4-9)	0.202
Mental	7.92 ± 2.18 (4-13)	6.78 ± 2.05 (4-10)	**0.036**
General	10.85 ± 2.41 (7-14)	6.89 ± 2.57 (4-12)	**0.002**
Reduced Activity	6.62 ± 1.94 (4-9)	4.89 ± 1.17 (4-7)	**0.045**
Reduced Motivation	7.23 ± 2.68 (4-14)	4.89 ± 1.36 (4-8)	**0.007**

Our Question:

Do the changes in fatigue scores across the week correspond to parameters assessed in a clinical examination?

Hydration Status (n=21*)
Urine Specific Gravity & Plasma Volume

	Sunday M ± SD *(Range)*	**Tuesday** M ± SD *(Range)*	**Thursday** M ± SD *(Range)*	***p*-value Baseline to Final**
Urine Specific Gravity	1.021 ± 0.009 *(1.002-1.036)*	1.020 ± 0.009 *(1.004-1.040)*	1.017 ± 0.008 *(1.004-1.032)*	0.162
Calculated Plasma Volume (liters)	3.11 ± 0.36 *(2.37-3.90)*	3.06 ± 0.34 *(2.37-3.90)*	3.07 ± 0.32 *(2.37-3.69)*	0.155

** n=21 due to one missing urine sample at baseline*

- Calculated plasma volumes were within range of euhydration (2.98 - 3.19 L)
- Baseline urine specific gravity suggested very mild dehydration (> 1.020)
- Midweek and study endpoints were within range of euhydration to hypohydration (≥ 1.013 to ≤ 1.020)
- No significant change in hydration status across the study period.

Blood Chemistry (N=22)

Analyte (mmol/L)	**Sunday** M ± SD *(Range)*	**Tuesday** M ± SD *(Range)*	**Thursday** M ± SD *(Range)*	***p*-value Baseline to Final**
Sodium (Na)	140.09 ± 1.72 *(135-142)*	140.14 ± 1.61 *(137-143)*	140.32 ± 1.32 *(138-144)*	0.64
Potassium (K)	3.84 ± 0.29 *(3.4-4.6)*	3.95 ± 0.22 *(3.5-4.4)*	3.89 ± 0.16 *(3.7-4.2)*	0.54
Chloride (Cl)	103.00 ± 2.43 *(99-109)*	102.00 ± 2.31 *(98-107)*	102.23 ± 2.49 *(98-109)*	0.15
Ionized Calcium	1.27 ± 0.04 *(1.2-1.36)*	1.27 ± 0.03 *(1.22-1.36)*	1.27 ± 0.03 *(1.22-1.33)*	0.83
Total Carbon Dioxide	25.09 ± 1.97 *(22-29)*	25.32 ± 1.81 *(23-28)*	25.45 ± 1.95 *(22-30)*	0.28
Anion Gap	16.82 ± 2.22 *(9-19)*	17.77 ± 1.02 *(16-20)*	17.59 ± 0.96 *(15-19)*	0.39
Lactate	1.09 ± 0.36 *(0.5-2.0)*	0.89 ± 0.32 *(0.5-1.7)*	1.01 ± 0.49 *(0.5-2.8)*	0.34

Blood Chemistry (N=22) *(continued)*

Analyte (mmol/L)	**Sunday** M ± SD *(Range)*	**Tuesday** M ± SD *(Range)*	**Thursday** M ± SD *(Range)*	***p*-value Baseline to Final**
Glucose (mg/dL)	95.00 ± 11.16 *(75-125)*	98.55 ± 14.69 *(85-145)*	98.68 ± 14.61 *(85-134)*	0.28
Blood Urea Nitrogen (mg/dL)	19.23 ± 6.43 *(7-34)*	17.73 ± 3.88 *(8-27)*	17.09 ± 4.37 *(9-27)*	0.15
Creatinine (mg/dL)	1.10 ± 0.25 *(0.6-1.8)*	1.01 ± 0.21 *(0.7-1.4)*	1.02 ± 0.19 *(0.7-1.5)*	0.20
Hematocrit (%PCV)	42.91 ± 3.28 *(35-48)*	43.82 ± 2.02 *(41-47)*	43.50 ± 2.63 *(38-48)*	0.28
Hemoglobin (g/dL)	14.59 ± 1.11 *(11.9-16.3)*	14.89 ± 0.68 *(13.9-16.0)*	14.79 ± 0.90 *(12.9-16.3)*	0.27

No changes in blood chemistry values across the study period.

Pulmonary Function Tests (N=22)
Spirometry

	Sunday M ± SD *(Range)*	**Tuesday** M ± SD *(Range)*	**Thursday** M ± SD *(Range)*	***p*-value Baseline to Final**
Forced Vital Capacity (FVC)	5.41 ± 0.87 *(3.9-7.2)*	5.28 ± 0.77 *(3.6-6.8)*	5.32 ± 0.78 *(3.9-7.1)*	0.64
Forced Expiratory Volume (FEV1)	4.17 ± 0.52 *(3.3-5.5)*	4.13 ± 0.45 *(3.2-5.1)*	4.16 ± 0.54 *(3.2-5.5)*	0.85

No changes in pulmonary function tests across the study period.

Summary

- Mean age in our cohort was late 30s with BMI ~ 26
- Measures of hydration status did not change across the study period. Results of Urine Specific Gravity, Calculated Plasma Volume, and Hematocrit suggest dehydration was not a factor contributing to fatigue.
- Blood chemistry values did not change across the study period
- Pulmonary function did not change across the study period
- **However, 20 of 42 blood serum analyte levels did change significantly across the study.**

Conclusion

- Neither physical examination findings, blood chemistry, pulmonary function tests, nor urine specific gravity corresponded with increased levels of fatigue.
- This suggests a mechanism other than an apparent underlying chronic pathology or acute subclinical illness contributed towards the onset of fatigue.
- These findings argue against an infectious etiology for the onset of fatigue

- **Results of serum analytes and their relationship with fatigue will be discussed next**

Thank you for your time and attention!

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