The Relationship Between Fatigue and Cardiac Functioning

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Background: Although characteristics such as heart rate (HR) and blood pressure (BP) are commonly reported in studies of the relationship between fatigue and cardiac functioning, few reports examine how cardiac function parameters such as cardiac output (CO) and stroke volume (SV) relate to fatigue. This study examined the relationship between self-reported fatigue and hemodynamic functioning at rest and in response to a public speaking stressor in healthy individuals.

Methods: A total of 142 individuals participated in this study. Subjects were placed in low-, moderate-, or high-fatigue groups based on their Profile of Moods State (POMS) fatigue scale. Heart rate, SV, and CO were determined using impedance cardiography at rest and during a speaking stressor. Stroke volume and CO values were converted to stroke index (SI) and cardiac index (CI) by adjusting for body surface area. Data were analyzed with hierarchical regression analysis and a 3 (group) × 3 (stress period) mixed model analysis of variance.

Results: At rest, fatigue was not associated with BP or HR but was significantly associated with decreased CI (P < .001; 95% confidence interval, −0.046 to −0.014) and stroke index (SI) (P = .002; 95% confidence interval −0.664 to −0.151), even after controlling for demographic variables and depressive symptoms. Heart rate and BP increased, as expected, from baseline to preparation to speaking stressor (F1,124 = 118.6 and F1,122 = 46.450, respectively) (P < .001 for both). More interestingly, there were effects on SI and CI of fatigue (P < .03 for both) and stress (P < .03 for both); high-fatigue individuals had lower SI and CI levels than moderate- and low-fatigue individuals both at rest and in response to the stressor.

Conclusion: This study demonstrates that fatigue complaints may have hemodynamic correlates even in ostensibly healthy individuals.

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Fatigue is one of the most commonly encountered complaints in medical practice. It is characterized by a lessened capacity or motivation for work and is usually accompanied by feelings of weariness and sleepiness. Fatigue is a nonspecific symptom associated with many medical conditions such as hypothyroidism, celiac disease, anemia, influenza, heart failure, and sleep apnea. It is the defining symptom in chronic fatigue syndrome (CFS) and is one of the most distressing symptoms associated with chemotherapy. Fatigue is also a common complaint of many veterans of the Gulf War of the 1990s. In most instances, the precise mechanism of fatigue is not well understood.1-7

Recent reports have found disturbances in autonomic and immune activity in patients with CFS.8,9 Using tests of heart rate variability with deep respiration, blood pressure (BP) decrease on tilting, heart rate (HR) increase with postural change, and resting HR, Freeman and Komaroff10 found that patients with CFS had lower amplitude change than healthy controls in HR variability with deep respiration, HR increase with postural change, and BP decrease on tilting. Numerous other studies of stress response in patients with fatigue reveal subtle changes in autonomic nervous system activity.3,9,14

Given the symptoms associated with fatigue, it is natural to wonder if cardiac function is altered in the presence of high fatigue levels from whatever cause. Unfortunately, studies examining the relationships between cardiac function and fatigue are rare, although some studies suggest that excessive fatigue may be an early manifestation of heart failure.15,16 In a study examining hemodynamic functioning in patients with CFS, it was found that patients with severe CFS had significantly lower stroke volume (SV) and cardiac output (CO) than the controls and less ill patients.17,18 Instead of studying cardiac function directly, most studies of fatigue and cardiovascular physiology focus on more readily measurable variables such as HR, HR variability, and BP.
A recent article by Choi et al. found that sleepiness levels were related to CO in a sample of patients with obstructive sleep apnea but with no known cardiac disease. Individuals who reported more sleepiness had lower CO and SV. These findings implied that complaints such as sleepiness may not just reflect subjective distress but may also be an early marker of cardiac impairment. Might this observation apply to healthy controls as well?

Given the work on autonomic nervous system functioning in CFS and the findings that sleepiness is associated with lower CO in patients with obstructive sleep apnea, we wondered if complaints of fatigue might be associated with altered SV and CO, even in healthy subjects. We also wondered if these noninvasive measures of cardiac hemodynamic functioning may be more sensitive to fatigue's effects than measures of HR or BP.

### Methods

#### Subjects

One hundred forty-two volunteers (47% women, 46% black, and 20% with hypertension) participated in this study. Subjects were either healthy volunteers or patients with mild to moderate hypertension who were not receiving antihypertensive medication.

We excluded patients with a prior diagnosis or treatment of diabetes, a fasting blood glucose level higher than 120 mg/dL, patients with congestive heart failure, bronchospastic pulmonary disease, symptomatic coronary or cerebral vascular disease (history of myocardial infarction, angina, stroke, or transplant ischemic attack), history of life-threatening arrhythmias, cardiomyopathy, history of psychosis, current drug abuse, or current alcohol abuse (supported by history or elevated findings on liver function tests). We excluded patients who had received psychotropic medications, patients with known secondary hypertension, those with creatinine levels higher than 1.4 mg/dL, proteinuria, hematuria, or renal bruit found on physical examination. Women accepted for the study were not taking contraceptives, nor were they pregnant. Characteristics of the subjects are summarized in Table 1. The protocol was developed by the institutional review board of the University of California San Diego, and subjects entered the study after giving informed consent.

### Procedure

Participants were admitted to the General Clinical Research Center of the University of California San Diego the night prior to the testing day. They completed the mood self-report using the Profile of Mood States (POMS) while resting comfortably the evening before testing. The POMS is a self-administered, adjective rating scale that measures 6 dimensions of mood: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, confusion-bewilderment, and fatigue-inertia during the past week. The normative data indicate a mean (SD) score of 7 (6). The POMS has been used in a variety of chronically ill populations, including groups with obstructive sleep apnea, as well as in healthy populations. The present study focuses on the fatigue-inertia subscale, which measures weariness, inertia, and low energy levels.

Cardiovascular reactivity testing, as a way to perturb the heart and autonomic nervous system, was performed on the morning of the testing day. Blood pressure data were collected continuously with a Colin Pilot radial tonometric noninvasive blood pressure monitor (Colin Instruments, Houston, Texas). Heart rate was determined by electrocardiography. Stroke volume was determined with impedance cardiography, and CO was calculated.

To record the impedance cardiography measurements, an impedance cardiographic tape was applied in a tetrapolar configuration. The Z2 electrode was attached around the base of the neck just superior to the suprasternal notch of the thorax. The Z1 electrode was placed 3 cm above the Z2. Electrode Z3 used the xiphoid process as an anatomic landmark. The electrode tape was placed over the xiphoid process circumscribing the thorax, and the tape was kept parallel to the floor. The Z4 electrode was placed about 10 cm below and parallel to the Z3. The distance between the Z2 and Z3 was also determined while the subject was standing. After application of the impedance cardiographic electrode, the electrocardiograph electrodes were applied in a modified lead 1 or lead 2 configuration that maximized the P wave.

The signals were relayed to an analog-to-digital converter sampling at 1 kHz per channel and stored in a desktop personal computer. The dZ and Zo calibration signals were also stored in the computer for later conversion of the dZ/dt to μV/s and SV derivation. These data were collected in 3-minute epochs. The samples were ensemble averaged by a computer program (University of Miami, Behavioral Medicine Research Center, Coral Gables, Florida) that summed the digitized beat-by-beat waveforms, time synchronized to the R wave of the electrocardiogram, and divided by the number of cardiac cycles. The ensemble average was then graphically displayed, and the waveform events were scored by computer signal processing techniques using University of Miami, Behavioral Medicine Research Center software. Stroke volume was calculated using the Kubicek formula. The resting data were collected after the participant had been seated in a recliner chair for 30 minutes after instrumentation. Stroke volume and CO were converted to SI and CI by appropriate adjustment of body surface area.

For the cardiovascular reactivity testing, subjects were attached to the instruments at 9 AM and then allowed to sit quietly for 30 minutes for habituation to the instrumentation and testing environment. A 3-minute baseline was obtained at the end of the habituation period. After a 3-minute baseline period, the subjects were given instructions for a speaking task that involved preparing and presenting a speech in response to being falsely accused of shoplifting. Instructions noted that the perfor-

### Table 1. Characteristics of Study Participants at Screening

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low Fatigue</th>
<th>Moderate Fatigue</th>
<th>High Fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F</td>
<td>23/21</td>
<td>36/22</td>
<td>16/24</td>
</tr>
<tr>
<td>Ethnicity, B/W</td>
<td>18/26</td>
<td>28/32</td>
<td>22/18</td>
</tr>
<tr>
<td>Hypertension status, N/H</td>
<td>39/5</td>
<td>45/13</td>
<td>30/10</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>124 (1.83)</td>
<td>127 (2.03)</td>
<td>128 (2.47)</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>73 (1.45)</td>
<td>76 (1.30)</td>
<td>77 (1.78)</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>74 (1.57)</td>
<td>71 (1.55)</td>
<td>77 (1.70)</td>
</tr>
<tr>
<td>Age, y</td>
<td>36 (1.16)</td>
<td>37 (1.10)</td>
<td>38 (1.14)</td>
</tr>
<tr>
<td>BMI</td>
<td>26.65 (0.86)</td>
<td>26.36 (0.79)</td>
<td>28.06 (1.02)</td>
</tr>
</tbody>
</table>

Abbreviations: B, black; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; W, white; N, normotensive; H, hypertensive.

*Data are reported as number of participants or mean (SEM) value; no significant differences were found in screening characteristics among the 3 fatigue groups.*
Manic tank was videotaped and rated by experts on poise and articulation. The video camera was displayed prominently during the preparation period. Subjects were given 3 minutes to prepare their speech and told that the speech should cover certain points. Immediately after the preparation period, subjects spoke for 3 minutes. If a subject stopped talking before the end of the period, he or she was reminded to continue the talk by reiterating or summarizing the main points. This speech stressor has been used extensively in our laboratory and other laboratories and elicits reliable changes in the measured parameters.14,24

To test our hypothesis that fatigue would predict SI and CI but not BP or HR, we performed a hierarchical regression analysis. In separate runs we placed SI, CI, HR, and mean arterial pressure (MAP) as dependent variables against a set of demographic variables in the first block (ethnicity, sex, age, and screening BP). The POMS fatigue score was then entered on step 2. The POMS depression score was entered on step 3 to examine the possibility that depressive symptoms might account for the findings concerning fatigue.

For illustrative purposes, POMS fatigue tertiles were created, and analyses of variance were performed. Individuals with POMS fatigue scores lower than 3 were classified as having low fatigue; those with scores between 3 and 7 were considered to have moderate fatigue; and those with scores higher than 7 were considered to have high fatigue. The dependent variables were MAP, CI, SI, and HR. These data were analyzed using a 3 × 3 mixed model analysis of variance (high vs moderate vs low fatigue group by baseline, preparation, and speaking stress period) (SPSS for Windows, version 12.0; SPSS, Chicago, Illinois). All P values are reported using the orthogonal trend method for repeated measures; Bonferroni corrections were made where appropriate.

**RESULTS**

Resting baseline measures of SI, CI, BP, and HR in relation to fatigue

Fatigue did not predict MAP or HR (data not shown). As summarized in Tables 2, 3, 4, and 5, fatigue was a significant predictor of SI and CI. Fatigue uniquely accounted for approximately 6% of the variance in SI and 8% of the variance in CI. The fatigue effects were independent of demographic variables such as age, ethnic-

### Table 2. Summary of Hierarchical Regression of Stroke Index

<table>
<thead>
<tr>
<th>Step</th>
<th>R</th>
<th>R²</th>
<th>Adjusted R²</th>
<th>SEE</th>
<th>Change in R²</th>
<th>Change in F</th>
<th>df</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>0.268</td>
<td>0.072</td>
<td>0.047</td>
<td>15.314</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Step 2</td>
<td>0.361</td>
<td>0.130</td>
<td>0.100</td>
<td>13.876</td>
<td>0.058</td>
<td>9.860</td>
<td>1.147</td>
<td>.002</td>
</tr>
<tr>
<td>Step 3</td>
<td>0.364</td>
<td>0.133</td>
<td>0.097</td>
<td>14.904</td>
<td>0.003</td>
<td>0.451</td>
<td>1.146</td>
<td>.503</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; SEE, standard error of the estimate.

For a detailed description of the 3 steps, see the “Procedure” subsection of the “Methods” section.

**Table 3. Prediction of Stroke Index Based on Hierarchical Regression Analysis**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>B</th>
<th>SEE</th>
<th>β Level</th>
<th>t Test</th>
<th>P Value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td>-1.593</td>
<td>2.554</td>
<td>-0.051</td>
<td>-0.624</td>
<td>.53 (-6.640 to 3.454)</td>
</tr>
<tr>
<td>Sex</td>
<td>0.773</td>
<td>2.538</td>
<td>0.025</td>
<td>0.304</td>
<td>.76 (-2.233 to 5.788)</td>
</tr>
<tr>
<td>Age in years</td>
<td>-0.416</td>
<td>0.163</td>
<td>-0.206</td>
<td>-2.551</td>
<td>.01 (-0.739 to -0.094)</td>
</tr>
<tr>
<td>Screening BP</td>
<td>-0.564</td>
<td>0.339</td>
<td>-0.134</td>
<td>-1.665</td>
<td>.10 (-1.234 to 0.106)</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td>0.027</td>
<td>2.534</td>
<td>0.001</td>
<td>0.011</td>
<td>.99 (-4.980 to 5.035)</td>
</tr>
<tr>
<td>Sex</td>
<td>-1.791</td>
<td>2.597</td>
<td>-0.057</td>
<td>-0.690</td>
<td>.49 (-6.923 to 3.341)</td>
</tr>
<tr>
<td>Age in years</td>
<td>-0.263</td>
<td>0.166</td>
<td>-0.130</td>
<td>-1.585</td>
<td>.12 (-0.739 to -0.094)</td>
</tr>
<tr>
<td>Screening BP</td>
<td>-0.462</td>
<td>0.331</td>
<td>-0.110</td>
<td>-1.396</td>
<td>.17 (1.116 to 0.192)</td>
</tr>
<tr>
<td>POMS fatigue</td>
<td>-0.407</td>
<td>0.130</td>
<td>-0.276</td>
<td>-3.140</td>
<td>.002 (-0.663 to -0.151)</td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td>-0.211</td>
<td>2.563</td>
<td>-0.007</td>
<td>-0.082</td>
<td>.93 (-5.277 to 4.855)</td>
</tr>
<tr>
<td>Sex</td>
<td>-1.654</td>
<td>2.610</td>
<td>-0.053</td>
<td>-0.634</td>
<td>.53 (-6.812 to 3.504)</td>
</tr>
<tr>
<td>Age in years</td>
<td>-0.259</td>
<td>0.166</td>
<td>-0.128</td>
<td>-1.559</td>
<td>.12 (-0.588 to 0.069)</td>
</tr>
<tr>
<td>Screening BP</td>
<td>-0.604</td>
<td>0.393</td>
<td>-0.144</td>
<td>-1.535</td>
<td>.13 (-1.382 to 0.173)</td>
</tr>
<tr>
<td>POMS fatigue</td>
<td>-0.408</td>
<td>0.130</td>
<td>-0.276</td>
<td>-3.138</td>
<td>.002 (-0.664 to -0.151)</td>
</tr>
<tr>
<td>POMS depression</td>
<td>0.197</td>
<td>0.293</td>
<td>0.063</td>
<td>0.672</td>
<td>.50 (-0.383 to 0.776)</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; CI, confidence interval; POMS, Profile of Mood States20; SEE, standard error of the estimate.

For a detailed description of the 3 steps, see the “Procedure” subsection of the “Methods” section.

b F₁₀,₁₄₈=2.856 (P=.03).
c F₁₀,₁₄₇=4.394 (P=.001).
d F₁₀,₁₄₆=3.723 (P=.002).
ity, sex, or screening BP. For explaining SI as well as CI, fatigue nearly doubled the variance explained by the demographic variables (\(P = .002\) and \(P = .001\), respectively). Adding depressive symptoms in a third step did not significantly increase the predictive capacity of the model, nor did it detract from the power of fatigue to explain CI and SI.

Figure 1 graphically portrays the fatigue effects on hemodynamic functioning at rest.

STRESS EFFECTS ON BP, HR, CI, AND SI IN RELATION TO FATIGUE

As seen in Figure 2, there was a significant stress effect for MAP (\(F_{1,118} = 46.5; P < .001\)) and heart rate (\(F_{1,118} = 118.6; P < .001\)) such that HR increased significantly from baseline to speech preparation to speech delivery (\(P < .001\) for all). Mean arterial pressure increased significantly from baseline to preparation to speaking (\(P < .001\) for all). No significant differences were found in HR or BP response between the various fatigue groups, nor was there a significant group-by-period interaction observed for MAP or HR.

As seen in Figure 3, there were significant stress effects on SI (\(F_{1,118} = 8.80; P < .001\)) and on CI (\(F_{1,117} = 6.53; P < .02\)). There was also a significant effect of fatigue on SI (\(F_{2,118} = 4.82; P = .02\)) and CI (\(F_{2,117} = 2.22; P = .002\)). The high-fatigue group had significantly lower levels of SI than the moderate-fatigue group or the low-fatigue group (\(P = .03\) and \(P = .02\), respectively). No significant differences were found between moderate- and low-fatigue groups.

Cardiac index increased significantly from baseline to preparation (\(P = .02\)) but showed no further change from preparation to talking. The high-fatigue group had significantly lower levels of CI than the moderate-fatigue group (\(P = .03\) and \(P = .02\), respectively). No significant differences were found between moderate- and low-fatigue groups.

We found that decreased SI and CI are related to higher fatigue at rest and during acute stress in healthy indi-
individuals. These findings are similar to what other researchers have found in patients with chronic fatigue and in veterans with Gulf War syndrome. The changes in hemodynamic function are subtle, certainly not in the recognized pathological range. However, these subtle changes were significantly associated with complaints of fatigue in reasonably healthy individuals.

These findings suggest that fatigue has a measurable relationship with cardiac functioning. There were no significant fatigue effects on simple measures such as HR or BP. However, fatigue had significant effects on hemodynamic measures of CI and SI. Measuring CI and SI is not typically part of the medical examination; thus, physicians may mistakenly conclude on the basis of routine

Figure 1. Resting levels of mean arterial pressure (MAP) (A), heart rate (B), stroke index (C), and cardiac index (D) by levels of fatigue as determined by the Profile of Mood States fatigue scale. The groups were created by dividing the scale into tertiles. Error bars indicate SEM.

Figure 2. Mean arterial pressure (MAP) and heart rate responses; error bars indicate SEM. A, Mean arterial pressure at baseline, during speech preparation, and during speaking periods. The high-fatigue group shows a significantly higher MAP than the moderate- and low-fatigue groups. There was no group × task interaction. B, Heart rate at baseline, during speech preparation, and during speaking periods. All 3 measures increased significantly in response to the stressor from baseline to preparation to speaking.
office screening that there is no cardiovascular disease accounting for fatigue.

There are several limitations of this study that should be taken into consideration. One limitation deals with our use of impedance cardiography to measure cardiovascular activity. This technique tends to underestimate SI and CI but tracks relative changes well. Replicating these observations with other measures such as echocardiography would be helpful.

Table 1 reveals that roughly 33% of moderate-fatigue and high-fatigue subjects had hypertension, whereas only about 15% of the low-fatigue subjects did (P = .23). The link between fatigue and BP is hardly straightforward; investigators have also found that fatigue is associated with lower BP. Even in the absence of a significant effect of hypertension status on fatigue, one might wonder if our observations on fatigue in relation to CI and the other parameters are being driven by hypertension. We reanalyzed the data using BP as a covariate and still observed the prominent effects of fatigue on SI and CI, even after controlling for BP (Tables 2, 3, 4, and 5).

Similarly, the POMS might not be an ideal measure of fatigue. The fatigue subscale is widely used measure of fatigue but does not assess specific dimensions of fatigue. Other measures such as the Multidimensional Fatigue Symptom Inventory could be used to examine specific aspects of fatigue such as physical, emotional, or mental fatigue. Since complaints of fatigue are so common and so nonspecific, use of more refined fatigue inventories may facilitate better understanding of the fatigue symptom setting that is associated with decreased cardiac functioning.

We did not evaluate sex or ethnic differences because the subgroup sample size would have been so small that the findings might have been unstable, given our statistical approaches. Future studies might include these factors. For instance, both social class and ethnicity influence complaints of fatigue. Because African Americans have increased rates of cardiovascular disease, it might be important to examine ethnic differences in future studies of fatigue and hemodynamic functioning. It would also be interesting to see if these findings are found in other patient groups for whom fatigue is a symptom (eg, patients with cancer). On the other hand, an advantage of this study was its focus on reasonably healthy individuals. With such a design, one minimizes potential confounding factors such as anemia, thyroid disease, or medications, which could affect both hemodynamic functioning and fatigue levels.

Is fatigue a prodrome of decreased hemodynamic functioning? This study suggests that there may be hidden cardiovascular manifestations of fatigue, even in healthy subjects. It remains to be seen whether the fatigue and/or stress effects on cardiovascular functioning observed herein are even stronger in patients with known cardiovascular disease. Similarly, the findings provide interesting context to studies reporting beneficial effects of exercise on both cardiovascular deconditioning and fatigue.

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Author Contributions: Dr Dimsdale had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Nelesen and Dimsdale. Acquisition of data: Nelesen and Dar. Analysis and interpretation of data: Nelesen, Thomas, and Dimsdale. Drafting of the manuscript: Nelesen, Dar, Thomas, and Dimsdale. Critical revision of the manuscript for important intellectual content: Nelesen and Dimsdale. Statistical analysis: Thomas. Obtained funding: Dimsdale. Administrative, technical, and material support: Nelesen, Dar, and Dimsdale. Study supervision: Dimsdale.
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REFERENCES