Title

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Journal

European Journal of Cardiovascular Nursing, 13(3)

ISSN

1474-5151

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Publication Date

2014-06-01

DOI

10.1177/1474515113482805

Peer reviewed

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Eur J Cardiovasc Nurs published online 22 March 2013
DOI: 10.1177/1474515113482805

European Journal of Cardiovascular Nursing

EUROPEAN SOCIETY OF CARDIOLOGY®

Original Article

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0(0) 1–10

DOI: 10.1177/1474515113482805
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Abstract

Background: Exhaustion, a consequence of prolonged stress characterized by unusual fatigue, is associated with increased risk of cardiac morbidity and mortality. In patients recovering from coronary artery bypass (CABG), little is known about the relationship of 1) immune-mediated inflammation and resultant endothelial activation, and 2) cumulative exposure to infectious pathogens (pathogen burden (PB)) implicated in coronary atherosclerosis to exhaustion.

Aim: The aim of this exploratory study was to investigate the association of PB, inflammatory markers (interleukin (IL)-6, IL-10) and a marker of endothelial activation (soluble intercellular adhesion molecule-1 (sICAM-1)) to exhaustion.

Methods: One to two months post-CABG, 42 individuals who met inclusion criteria were assessed for exhaustion using the Maastricht Interview for Vital Exhaustion. Serum IgG antibodies to herpes simplex virus (HSV)-1, HSV-2, cytomegalovirus, Epstein Barr virus, and inflammatory and endothelial activation markers were measured by enzyme-linked immunosorbent assay. Pathogen burden was defined as the total number of seropositive exposures: low (0-1), moderate (2-3), and high (4).

Results: Prevalence of exhaustion was 40.5%. Relative to non-exhausted patients, exhausted patients demonstrated a higher frequency of moderate PB (h=0.73, p=0.04) but lower frequency of high PB (h=1.05, p=0.03). Exhaustion showed a non-significant trend for positive correlations with IL-6 and sICAM-1 levels, and inverse relation to PB. In subgroup analysis, exhausted patients had stronger correlations with IL-6 and IL-6:IL-10 and a tendency towards higher serum IL-10 concentrations compared with their non-exhausted counterparts.

Conclusion: This hypothesis-generating study provides preliminary evidence that elevated post-CABG exhaustion may be associated with PB, inflammation, and endothelial activation.

Keywords

Coronary heart disease, cytokines, herpesviruses, inflammation, pathogen burden, vital exhaustion

Date received 4 December 2012; revised 21 February 2013; accepted 26 February 2013

Vital exhaustion (hereafter referred to as exhaustion) is characterized by unusual fatigue, general malaise, irritability and demoralization,[1] and predicts long-term risk of incident myocardial infarction and fatal coronary heart disease (CHD).[2] Increasing evidence suggests that exhaustion is a complex state that involves immunologic dysregulation,[3-5] and has been described among individuals who demonstrate an inability to cope with prolonged stress.[6] Several studies have reported strong correlations between depressive symptoms and exhaustion,[7,8] specifically somatic symptom overlap.[9] Inflammatory mechanisms underlying CHD have been similarly recognized as contributing to the pathogenesis of depression[10] as well as exhaustion.

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Viral infections, inflammation, and endothelial dysfunction have been implicated in atherogenesis. The presence of lifelong, latent herpesviruses in atherosclerotic plaque may exert pathogenetic effects by penetrating the arterial wall, modifying lipid metabolism, and stimulating the production of pro-inflammatory cytokines and growth factors.[11] Cumulative exposure (i.e. seropositivity) to multiple infectious pathogens known as pathogen burden (PB) is associated with elevations in CHD risk, inflammation, and endothelial dysfunction. Chronic, pathogen-induced inflammation may be a key process whereby PB has been linked to atherosclerotic disease progression and increased risk of future cardiac death.[12] Interleukin(IL)-6 is a pleiotropic cytokine involved in atherogenesis and has independent predictive value for future cardiac events.[13] Prior research on the role of anti-inflammatory IL-10 has been less clear, suggesting IL-10 was associated with both decreased and increased risk of mortality and adverse cardiac events.[14,15] Intercellular adhesion molecule-1 (ICAM-1) is a pivotal vascular glycoprotein involved in inflammatory cell recruitment and endothelial activation in atherosclerosis. Elevated levels of its soluble form (sICAM-1) have been associated with long-term risk of cardiovascular events in patients with stable CHD and acute coronary syndromes (ACS).[16,17]

Previous investigations have explored the relationship between exhaustion, infectious pathogens and immune variables. Exhaustion was significantly associated with increased levels of IL-1ra, IL-6, and IL-10 and higher seropositive levels of PB, specifically immunoglobulin (Ig)G antibodies to herpes simplex virus (HSV), cytomegalovirus (CMV), Epstein Barr virus (EBV), and varicella-zoster virus in healthy adults.[5] Exhausted patients with severe, stable angina pectoris post-directional coronary angiography expressed significant elevations in IL-1β, tumor necrosis factor-α, and CMV titers (IgG; IgM) as well as non-significant trends for higher IL-6 and *Chlamydia pneumoniae* IgG titer.[18] Exhaustion may function through mechanisms similar to psychological stress and depression by altering immune processes responsible for viral latency thereby stimulating herpesvirus reactivation.[19]

Patients undergoing coronary artery bypass graft (CABG) are characterized by advanced age, multivessel disease, and co-morbid burden (e.g. diabetes and heart failure). The CABG population remains at risk for cardiac-related mortality as a result of revascularization failure and the presence of new or progressive disease within the native coronary arteries or grafts, which manifests as ischemic symptoms and recurrent cardiac events (e.g. myocardial infarction).[20] Adverse cardiovascular outcomes after CABG may be linked to inflammatory pathology.[21,22] Expression of inflammatory and endothelial activation markers associated with PB may pose special risks (vulnerability) for CABG patients by inciting symptoms shared between depression and exhaustion (e.g. loss of energy, irritability, and sleep problems) which propagates CHD progression. Although the effects of immuno-inflammation and PB on CHD have been documented, it is not well understood whether these clinically relevant physiological processes impact elevations in exhaustion among CABG patients. To date, the expression of circulating levels of sICAM-1 as an index of endothelial dysfunction has not been explored within the context of exhaustion. The purpose of this hypothesis-generating, exploratory study was to investigate the relationship of PB (cumulative seropositivity to HSV-1 and 2, CMV, EBV), immuno-inflammatory markers (IL-6, IL-10) and a marker of endothelial activation (sICAM-1) to exhaustion. In addition, we examined associations between PB and immuno-inflammation among post-CABG adults.

Methods

Sample

In a cross-sectional, correlational design, a convenience sample of patients who were 45 years of age and older and underwent CABG were recruited from outpatient clinics and inpatient units in two cardiac centers at a university-affiliated public healthcare institution and federal tertiary care facility in Los Angeles, California between March 2008 and April 2009. Patients were excluded if they suffered with malignancy, autoimmune disorder, active infection, or current smoking, which have been demonstrated to alter the immune and inflammatory response.[23] None of the patients were being actively treated for mood or affective disorders.

Patients were recruited through flyers placed at cardiology and cardiac surgery outpatient practices and inpatient units at the recruitment sites. The clinical staff, comprising cardiologists, nurse practitioners, and nurses, identified potential patients who met eligibility criteria, informed patients about the study, and provided patients with a study flyer. Patients who were willing to learn more about the study were referred to the study investigator for an explanation of the study procedures.

A total of 205 patients were approached. Of the 169 eligible patients, 57 individuals gave informed consent and were enrolled. Reasons for declining to participate were related to postoperative recovery, out of state residence, inability to accommodate schedule, and lack of interest in the study. Fifteen enrolled subjects were either post-operatively deceased, lost to follow-up, ineligible to participate because of complications, or withdrew voluntarily from the study. However, when eligible patients who declined to participate were compared with the 42 patients who completed data collection, there were no baseline differences in sociodemographic and clinical characteristics. The Institutional Review Board of the participating sites approved the study protocol, and all patients provided written informed consent.

Procedure

Patients (age range: 45-99 years) underwent one study visit for data collection 4-8 weeks post-hospitalization discharge. Patients were given the 23-item Maastricht Interview for Vital Exhaustion (MIVE), a standardized measure for the presence of exhaustion, that includes questions regarding unusual fatigue, loss of energy, increased irritability, and feelings of demoralization.[24] Scoring was based on the presence or absence of the items in question, and ranged from 0 to 23. In the current study, Cronbach's alpha for the MIVE was 0.85, indicating good reliability. Patients were designated as exhausted if they endorse ≥7 out of 23 MIVE items.[25] Interviews from four randomly selected patients were audiotaped to monitor inter-rater reliability and were scored by a second clinician. The blinded assessment yielded an inter-rater agreement of 100% with respect to coding for individual MIVE items, total MIVE score, and exhaustion status for each patient. Medical records were used to obtain sociodemographic data, cardiovascular risk factors, pre-existing co-morbidities, and current medication regimen.

Laboratory analyses

Blood was drawn between 7am and 12pm in order to minimize the effects of physical activity and diurnal variation. Blood was initially clotted at room temperature for 15-30 minutes and then centrifuged at 1000 × *g*. All sera were stored at -80°C until further analysis. Prior to assaying, frozen sera was brought to room temperature slowly and gently mixed.

Thawed serum samples were used to qualify IgG antibodies to four pathogens: HSV-1, HSV-2, EBV (viral capsid antigen), and CMV. We used IgG antibodies based on prior evidence demonstrating increased risk of CHD morbidity and mortality and exhaustion from the cumulative effect of past exposures to pathogen infections (seropositivity) as opposed to active infections (e.g. IgM).[5,12,26] Antibodies to HSV, EBV, and CMV were measured using commercially available enzyme-linked immunosorbent assay (ELISA) methods (Inverness Laboratories, Princeton, NJ, USA (CMV, EBV) and Focus Diagnostics, Cypress, CA, USA (HSV)). The intra-assay coefficients of variation for all serological assays were < 7%. Index values were reported according to manufacturer specifications. Serum concentrations of IL-6, IL-10, and sICAM-1 were quantified by monoclonal antibody-based ELISA methods (Invitrogen, Carlsbad, CA, USA). The intra-assay coefficient of variation for all immuno-inflammatory assays was ≤ 15%.

All assays were performed in a single batch according to manufacturer instructions by a certified biosafety level-2 central laboratory to prevent inter-assay variation. Internal consistency was established by titrating duplicates of each standard and sample. Assays were quantified by spectrophotometry using the VersaMax Tunable Plate Reader and SoftMax® Pro microplate reader software.

To identify potentially confounding acute infections, complete blood count with differential was assessed using blood treated with ethylenediaminetetraacetic acid (AcT diff analyzer, Beckman & Coulter, Netherlands). If blood count for leukocytes was currently available in the medical record, then these laboratory values were used. No patients demonstrated evidence of active infectious process.

Statistical analyses

Computations were carried out using SPSS software, version 17.0 (SPSS Inc., Chicago, IL, USA). Independent sample t-test, chi-square test, and Fisher's exact test were used to compare exhausted and non-exhausted groups with continuous and categorical data, respectively. Pathogen burden was defined according to the total number of seropositive exposures: low (0−1), moderate (2−3), and high (4). Effect sizes were calculated as Cohen's *d* (mean differences) and Cohen's *h* (proportional differences) between exhausted and non-exhausted groups using comparable thresholds (0.2, small effect; 0.5, moderate effect; and 0.8, large effect). Pearson and partial correlation coefficients were used to analyze the relationships between exhaustion, PB, and immuno-inflammatory measures. Effect size (*r*) conventions were 0.1 for small, 0.3 for medium, and 0.5 for large effects.[27] Sociodemographic and clinical variables ($p<0.10$ in bivariate analyses) were included as covariates to control for possible confounding effects. Analyses for IL-6, IL-10, and sICAM-1 were determined based on natural log transformations. Approximately two-thirds (72.5%) of the samples were below the lower level of detection (0.781 pg/ml) for IL-10 by ultrasensitive ELISA. These undetectable levels were treated as left-censored, and assigned a value half that of the detection level to minimize bias concerning over- and under-estimation. The IL-6:IL-10 ratio for each subject was calculated using IL-10 imputations. Significance levels were based on two-tailed tests with a *p* value of 0.05. Trends towards significance ($p\leq0.10$) were acknowledged in order to identify correlates for additional exploration in subsequent studies and to minimize Type II errors that omit potential associations that may not be a result of chance.

Results

Sample characteristics

Exhaustion scores on the MIVE ranged from 0 to 19 (5.7±4.3). Prevalence of exhaustion was 40.5% ($n=17$; $p<0.001$) as defined by MIVE scores ≥ 7. These 17 subjects were categorized as the exhausted group for comparisons with the 25 subjects in the non-exhausted

Table 1. Sociodemographic and clinical characteristics.

Variable	Total Sample (n = 42)	Exhaustion (n = 17)	No exhaustion (n = 25)
	Mean ± SD	Mean ± SD	Mean ± SD
Age (years)	67.5 ± 12.6	63.4 ± 9.5	70.1 ± 13.7
Body mass index (kg/m^2)	27.6 ± 4.2	28.9 ± 4.3	26.8 ± 3.0
Highest percentage of stenosis	89.6 ± 12.6	89.7 ± 12.4	89.5 ± 13.0
Total # of bypass grafts	3.12 ± 1.3	3.5 ± 1.2	2.9 ± 1.3
	N (%)	*N* (%)	*N* (%)
Gender			
Male	38 (90.5)	17 (100)	21 (84)
Race			
Caucasian	28 (66.7)	10 (58.8)	18 (72)
Education			
Bachelor's or graduate degree	22 (52.4)	10 (58.8)	12 (48)
Annual income			
$20,000–60,000	20 (47.6)	8 (47.1)	12 (48)
Marital status			
Married or cohabitating	27 (64.3)	15 (88.2)	12 (48)
Employment status			
Retired	23 (54.8)	7 (41.2)	16 (64)
Recruitment site			
University-affiliated	28 (66.7)	11 (64.7)	17 (68)
Federal tertiary	14 (33.3)	6 (35.3)	8 (32)
Co-morbid history			
Angina	25 (59.5)	13 (76.5)	12 (48)
Heart failure	7 (16.7)	2 (11.8)	5 (20)
Valvular disease	17 (40.5)	4 (23.5)	13 (52)
Myocardial infarction	14 (33.3)	6 (35.3)	8 (32)
CV risk factors			
Family history of CAD	10 (23.8)	6 (35.3)	4 (16)
Older than 65 years	20 (47.6)	5 (29.4)	15 (60)
Hypertension	36 (85.7)	15 (88.2)	21 (84)
Hyperlipidemia	34 (81)	15 (88.2)	19 (76)
Diabetes mellitus	23 (54.8)	10 (58.8)	13 (52)
Former tobacco use	29 (69)	14 (82.4)	15 (60)
Physical inactivity	31 (73.8)	13 (76.5)	18 (72)
Medications			
Aspirin	38 (90.5)	16 (94.1)	22 (88)
ACE inhibitors	17 (40.5)	8 (47.1)	9 (36)
Beta blockers	40 (95.2)	17 (100)	23 (92)
Clopidogrel	19 (45.2)	9 (52.9)	10 (40)
Hypoglycemics	14 (33.3)	6 (35.3)	8 (32)
Statins	38 (90.5)	15 (88.2)	23 (92)

ACE: angiotensin converting enzyme; CAD: coronary artery disease; CV: cardiovascular; SD: standard deviation.
Statistical analyses performed by independent sample t-test, chi-square test, and Fisher's exact test.

group. Table 1 displays sociodemographic and clinical characteristics of exhausted and non-exhausted subjects. There was a non-significant trend favoring exhausted patients as younger (d=–0.54, p=0.07), male (h=0.82, p=0.08) and married or cohabitating (h=0.90, p=0.09) with higher body mass index (d=0.58, p=0.08) and history of angina (h=0.61, p=0.07) compared with non-exhausted patients.

Pathogen burden

The distribution of IgG seropositive patients in the sample for each infectious pathogen is illustrated in Table 2. The percentages of patients exposed to a total of 0, 1, 2, 3, or 4 pathogens were 2.5%, 5%, 27.5%, 50%, and 15%, respectively. There were no group differences between exhausted and non-exhausted patients for IgG

Table 2. Two-group comparison: IgG seropositive status and pathogen burden.

Variable	Total seropositivity (n = 40)	Exhaustion (n = 16)	No exhaustion (n = 24)	p	ES (h)
	N (%)	*N* (%)	*N* (%)		
HSV-1	29 (72.5)	12 (75)	17 (70.8)	0.77	0.09
HSV-2	11 (27.5)	2 (12.5)	9 (37.5)	0.08[a]	−0.59
CMV	30 (75)	12 (75)	18 (75)	1.00	0
EBV VCA	38 (95)	15 (93.8)	23 (95.8)	0.77	−0.09
Pathogen burden (3 level variable)					
Low	3 (7.5)	1 (6.3)	2 (8.3)	0.08[a]	−0.08
Moderate	31 (77.5)	15 (93.8)	16 (66.7)		0.73
High	6 (15.0)	0	6 (25)		−1.05

CMV: cytomegalovirus; EBV VCA: Epstein Barr virus viral capsid antigen; ES: effect size; *h*: Cohen's *h*; HSV: herpes simplex virus.
Statistical analyses performed by chi-square test and Fisher's exact test.
[a]$p \leq 0.10$

seropositivity to HSV-1, CMV, or EBV VCA. Compared with non-exhausted patients, exhausted patients had a non-significant trend towards less IgG seropositivity to HSV-2. Low PB (0-1 exposures) was reported in 7.5% of the total sample, whereas moderate burden (2-3 exposures) and high burden (4 exposures) were identified among 77.5% and 15.0% of the total sample, respectively. Differences between exhausted and non-exhausted patients with moderate burden and high burden were statistically significant (Figure 1).

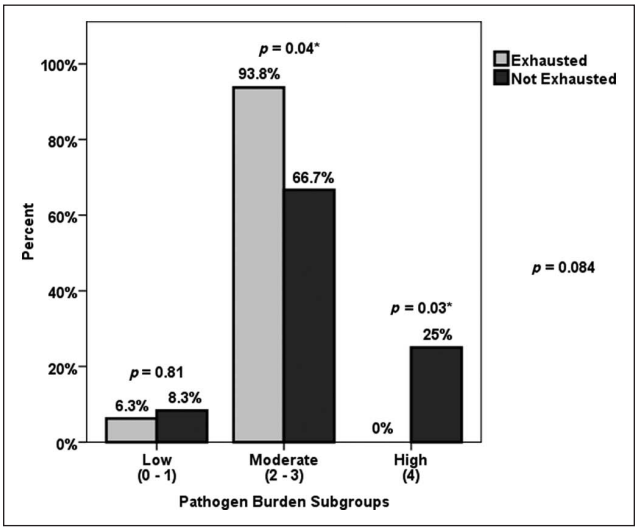

Figure 1. Distribution of pathogen burden by exhaustion status in post-CABG subjects. Bar graph illustrates proportional differences in exhaustion status tested using 2 × 3 (for all three levels of burden) and 2 × 2 (presence/absence for each level of burden) contingency tables. Differences between exhausted and non-exhausted subjects with moderate burden (93.8% vs. 66.7%, h = 0.73, p = 0.04) and high burden (0% vs. 25%, h = −1.05, p = 0.03) were statistically significant. There was a non-significant trend towards a difference in the levels of pathogen burden for exhausted and non-exhausted patients (p = 0.08). CABG, coronary artery bypass graft.

Immuno-inflammation and endothelial activation

Table 3 displays serum levels of IL-6, IL-10, and sICAM-1 between the two groups of patients. Mean serum levels of IL-6, IL-10, IL-6:IL-10 ratio, and sICAM-1 among exhausted patients were not statistically significant when compared with non-exhausted patients. However, there was a non-significant trend difference between exhausted and non-exhausted patients for the presence of low serum IL-10 concentrations.

A significantly moderate, positive correlation was observed between IL-6 and sICAM-1 (r=0.45, p=0.005). Significant relationships were not observed between serum IL-6, IL-10, IL-6:IL-10, or sICAM-1 concentrations and PB (continuous and categorical) (p>0.10). These relationships remained unchanged after controlling for the possible anti-inflammatory effects of medication use.

Pathogen burden, immuno-inflammation, and endothelial activation

Pearson's correlation coefficient and partial correlations are presented in Table 4. In the overall sample, correlations between exhaustion and IL-6 (unadjusted), sICAM-1 (gender-adjusted), and PB (age- or body mass index-adjusted) were non-significant trends ($p \leq 0.10$). On closer examination of subgroups, only circulating IL-6 and IL-6:IL-10 concentrations were strongly correlated in exhausted patients (IL-6, r=0.62, p=0.01; IL-6:IL-10, r=0.51, p=0.04), whereas these correlations were weaker or non-significant in non-exhausted patients (IL-6, r=0.44, p=0.04; IL-6:IL-10, r=0.14, p=0.53).

Table 3. Immuno-inflammatory and endothelial activation markers.

Variable	Exhaustion (n = 16)	No exhaustion (n = 24)	p	ES (d)
	Mean ± SD (median, IQR)	Mean ± SD (median, IQR)		
IL-6 (pg/ml)	3.2 ± 5.1 (1.65, 2.17)	2.15 ± 1.1 (1.93, 4.20)	0.92	0.31
Log-transformed IL-6	0.59 ± 0.99 (0.50, 1.33)	0.62 ± 0.58 (0.66, 0.78)		
IL-10 (pg/ml)	1.03 ± 0.93 (0.39, 1.17)	1.87 ± 6.3 (0.39, 0)	0.44	−0.17
Log-transformed IL-10	−0.33 ± 0.85 (−0.94, 1.38)	−0.57 ± 1.0 (−0.94, 0)		
IL-6:IL-10 ratio	4.44 ± 4.7 (2.00, 4.69)	4.67 ± 3.18 (4.27, 4.06)	0.43	−0.06
Log-transformed IL-6:IL-10	0.92 ± 1.18 (0.69, 1.60)	1.21 ± 1.05 (1.45, 1.07)		
sICAM-1 (ng/ml)	281.93 ± 69.58 (273.26, 127.07)	282.2 ± 89.3 (288.91, 124.23)	0.84	−0.003
Log-transformed sICAM-1	5.61 ± 0.26 (5.61, 0.44)	5.59 ± 0.34 (5.67, 0.45)		
	N (%)	*N* (%)	p	ES (*h*)
Low serum IL-10[b]	9 (56.3)	20 (83.3)	0.06[a]	−0.60

d: Cohen's *d*; ES: effect size; *h*: Cohen's *h*; IL: interleukin; IQR: interquartile range; SD: standard deviation; sICAM-1: soluble intercellular adhesion molecule-1.
Statistical analyses performed by independent sample t-test.
[a]$p \leq 0.10$

Table 4. Pearson's correlation coefficient between exhaustion and biological parameters, and partial correlations adjusted for age, gender, body mass index, and history of angina (n = 40).

	Un-adjusted	Age-adjusted	Gender-adjusted	BMI-adjusted
IL-6	0.30[a]	0.17	0.07	−0.001
IL-10	0.22	0.18	0.10	0.21
IL-6: IL-10	0.02	−0.07	−0.04	−0.19
sICAM-1	0.10	0.14	0.26[a]	0.12
PB	−0.18	−0.28[a]	−0.27	−0.28[a]

BMI: body mass index; IL: interleukin; PB: pathogen burden (total seropositive exposures); sICAM-1: soluble intercellular adhesion molecule-1.
Analyses conducted on log-transformed data.
[a]$0.05 < p \leq 0.10$.

Discussion

To our knowledge, relations of exhaustion with sICAM-1, IL-6, IL-10 and PB have not been examined in post-CABG patients. This exploratory study provides preliminary evidence that suggests exhaustion may be associated with increases in sICAM-1 and decreases in PB after CABG surgery, albeit as non-significant trends. Relative to non-exhausted patients, exhausted patients demonstrated a higher frequency of moderate PB but lower frequency of high PB. Findings also revealed a significant positive correlation of exhaustion with IL-6 and IL-6:IL-10. Exhausted patients tended to have higher serum IL-10 concentrations compared with their non-exhausted counterparts.

Counterintuitively, the high PB group was associated with lower exhaustion; whereas, the moderate PB group was associated with higher exhaustion. Although those who had the highest PB were not the most exhausted, it is likely that high burden may be associated with higher exhaustion in a larger sample with a greater distribution of patients across all PB levels, consistent with findings by van der Ven et al.[5] In comparison, when using our definition of PB, van der Ven and colleagues[5] demonstrated a larger effect difference between exhausted and control groups for moderate PB and high PB. Similarly, in a study by Miller et al.[26] of ACS patients who had myocardial infarction, CABG, or angioplasty, there was a significantly moderate effect between the number of seropositivities to latent herpesviruses and depressive symptoms. Moreover, the highest PB (three herpesviruses) was found among those with the highest depressive symptoms followed by middle and lowest depressive symptoms.[26] High PB is associated with promoting a pro-inflammatory, pro-coagulant and pro-atherogenic milieu with strong relative risk for CHD.[28,29] Furthermore, the relatively high seroprevalence and ubiquitous nature of EBV, CMV, and HSV-1 among CHD patients following CABG surgery may have created a 'ceiling' effect across the sample, contributing to poor distribution and less exposure variability. A broader range of previously studied obligate intracellular pathogens such as *Heliobacter pylori, Chlamydia pneumoniae* and hepatitis A[30] may be more informative.

A more compelling theoretical rationale for this discrepancy suggests that the relationship between exhaustion and PB may differ across sociodemographic strata. Prior research

linked higher PB with chronic stress and low socioeconomic status.[31] Exhaustion, described as a state of episodic distress (< 2 years),[32] has been reported to be higher in women, black people, and those with lower educational attainment.[2] The present study consisted of primarily Caucasian males who were socioeconomically advantaged. These patients were more likely to have a higher quality of social support and lower exposure to pathogens resulting in better immune function compared with their socioeconomically disadvantaged counterparts.[31,33] Therefore, the relationship between exhaustion and PB may have been attenuated by the sociodemographics of our sample.

Although there were no significant associations between PB and inflammatory markers, recent work by Nazmi et al.[30] indicates that defining PB according to antibody response levels to multiple pathogens as opposed to serostatus may reveal more robust relationships. The lack of association in our findings may be attributed, in part, to the higher socioeconomic status of the sample. Lower socioeconomic status is related to higher inflammation.[34] The interplay among host-specific factors (e.g. race/ethnicity, behavior and genetic background) may also influence the relationship between PB and inflammation.

There were no significant mean differences in IL-6, IL-10, IL-6:IL-10 and sICAM-1 between exhausted and non-exhausted groups. However, we identified correlations of elevated levels of circulating IL-6 and counter-regulatory IL-6:IL-10 ratio among exhausted individuals. Interleukin-6, a glycoprotein produced by lymphoid and non-lymphoid cells (e.g. T cells, macrophages, and endothelial cells), has an expansive and well-studied repertoire of biological functions, which includes pro- and anti-inflammatory properties that confer effects on Th1/Th2 and B cell differentiation and induction of acute phase C-reactive protein and other inflammatory mediators.[35] Previous studies reported divergent findings.[4,5,18] For example, van der Ven et al.[5] and Appels et al.[18] observed moderately large mean differences between exhausted and non-exhausted patients for IL-6[5,18] and IL-10,[5] suggesting that elevated IL-6 and IL-10 may mediate or contribute to exhaustion and low-grade chronic inflammation that characterizes coronary atherosclerosis. The fate of post-CABG exhaustion may be linked to disruption in the balanced expression of pro- and anti-inflammation as purported by mechanisms underlying atherosclerosis.

Our data indicated a non-significant trend difference in low serum IL-10 concentrations between exhaustion group contrasts. Interleukin-10, a pleiotropic anti-inflammatory cytokine secreted by various activated immune cells (e.g. T cells and macrophages), inhibits pro-inflammatory cytokine synthesis/release and antigen presentation and augments uptake of pathogens by macrophages/monocytes.[36] Alone or in combination with TGF-β, IL-6 enhances the production and release of IL-10 into the circulation, which, in turn, elicits suppressive effects on the pro-inflammatory response.[37] Clinical data have demonstrated reductions in serum IL-10 activity among patients with ACS,[38] suggesting a pro-inflammatory, pro-atherogenic state. Whereas, increases in IL-10 were associated with favorable prognosis for adverse cardiac events in ACS patients during 1-year follow-up,[39] suggesting an atheroprotective role. In contrast, exhaustion was associated with elevated levels of IL-10 in adults with cardiovascular risk factors for heart failure.[4] Furthermore, elevated baseline IL-6 and IL-10 increased the risk of late cardiac events among exhausted post-percutaneous coronary intervention patients.[3] Elevated IL-10 in exhaustion may suggest the presence of heightened systemic inflammation, whereas deficiency of IL-10 may suggest the existence of a persistent inflammatory response. Attenuated expression of IL-10 would potentiate unrepressed inflammation that leads to immune pathology and tissue damage.

A significant association of sICAM-1 with IL-6 and a non-significant trend with exhaustion were observed. Soluble ICAM-1 is derived from proteolytic cleavage of the transmembrane-bound ICAM-1 and found biologically active in serum. Produced by a variety of cells (e.g. vascular endothelial cells and hematopoietic cell lines), ICAM-1 is up-regulated by stimulated cytokines.[40] Interleukin-6-induced adhesion molecule expression facilitates transendothelial migration of inflammatory cells (e.g. leukocytes and lymphocytes) in the early and advance stages of atherogenesis and activation of pro-inflammatory processes such as cytokine production that augments the inflammatory milieu.[40] Furthermore, sICAM-1 has been shown to predict incident CHD.[41]

According to the literature, exhausted patients are distinguished by hyporeactivity of the hypothalamic-pituitary-adrenal (HPA) axis, which is prompted by exposure to prolonged stress and leads to hypocortisolemia, pro-inflammatory release of cytokines, and fatigue.[18,42] Herpesviruses may pathogenically modulate or accelerate inflammatory responses, and thus, may be essential contributors to multiple phases of atherogenesis and influence the development of exhaustion. Reactivation of latent herpesviruses within the vascular wall generates nuclear factor-κB activation, resulting in the synthesis of atherogenic cytokines and chemokines.[11] Initiation of the inflammatory cascade is known to attract immune cells, and induce expression of ICAM-1, which is shed by activated cells into its soluble form. Increased levels of sICAM-1 and resultant increases in endothelial activation may explain the association of exhaustion to new cardiac events. However, at present, our exploratory data do not provide these inferences.

Limitations

Potential limitations should be considered. First, our findings are preliminary and should be interpreted with caution; they are limited by the small convenience sample and cross-sectional design. As such, effect estimates were used to report outcomes given concerns with statistical power

and possibility of Type I and II error. Non-probability sampling precludes generalizability. Second, we had a sufficient number of women in the sample to reflect the normal prevalence of CABG patients in the general population; however, inclusion of more women would have enriched findings. Third, when compared with prior studies,[3,5,18] our sample was distinguished by advanced age, extent and severity of multivessel disease, and propensity for higher inflammatory and thrombotic burden which may place post-CABG patients at a greater disadvantage. Moreover, it is possible that the CABG procedure contributed to the state of exhaustion. However, prior work found no difference in exhaustion between pre-CABG and 4 weeks post-CABG; significant differences were not reported until 5-6 months post-CABG.[43] Co-morbidity may contribute to exhaustion, although no significant differences between groups were found.

Lastly, high prevalence of aspirin, beta blocker, and statin use may obscure or reduce post-CABG immuno-inflammatory concentrations; although the effect of these medications as covariates was non-significant. Results were also less likely to be influenced by post-CABG wound healing as the majority of data were collected between 6 and 8 weeks post-hospitalization discharge. Activation of inflammatory responses has been observed to occur up to 8 days post-operatively, with levels declining towards preoperative baseline at 30 days post-CABG with non-significant differences for inflammatory markers.[44]

Conclusion

Evidence in the literature remains inconclusive about the biological pathways that explain the variability of exhaustion in patients with existing CHD. Taken together, the present exploratory data posit the notion that inflammation and herpesvirus pathogens may be correlated with exhaustion after CABG. Future work should explore these suppositions using larger samples to confirm the validity of our findings and to further elucidate associations in greater detail.

Our findings should not be construed as practice-changing until more conclusive data are available. However, the results support early recognition of patients with exhaustion who are at risk for adverse cardiovascular morbidity and mortality. Development of novel nursing strategies aimed at ameliorating exhaustion symptoms may target inflammatory pathways that specifically attenuate immune activation as an achievable goal. In the future, immune-specific correlates of exhaustion may hold promise as clinically objective indicators of therapeutic response to interventions. A recent meta-analysis found that psycho-behavioral and stress management interventions had a moderate effect on reducing exhaustion among cardiac patients and adults in the community.[45] The extent to which these interventions may impact inflammatory indices in exhaustion is unclear. If empirically substantiated, targeting inflammation-related exhaustion may aid in lowering the risk of future cardiac events in a population of patients characterized by diffuse, complex multivessel CHD.

Acknowledgements

The authors wish to express sincere gratitude to the individuals who participated or assisted in this research, for their generous contribution of time, support, and effort.

Conflict of interest

None declared.

Funding

This work was supported by grants from the American Academy of Nurse Practitioners Foundation; Sigma Theta Tau International; and Veterans Affairs Pre-doctoral Nurse Fellowship. This work was carried out in the facilities of the UCLA AIDS Institute, which were supported, in part, by funds from the James B. Pendleton Charitable Trust and the McCarthy Family Foundation.

Implications for practice

- Exhaustion occurred in over one-third of the post-CABG sample, and was associated with increases in cytokine levels and presence of moderate pathogen burden 4-8 weeks after hospital discharge.
- Additional research is needed to clarify relationships between exhaustion, immune-mediated inflammation, and pathogen burden after CABG, and to develop effective treatment strategies that improve exhaustion and target immuno-inflammatory indices.
- Results support early recognition of patients with exhaustion who are at increased risk for adverse cardiovascular morbidity and mortality.

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