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# Pathways to Postoperative Hostility in Cardiac Patients

## Mediation of Coping, Spiritual Struggle and Interleukin-6

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### Abstract

Using structural equation modeling, we estimated major pathways from preoperative distress, indicated by anxiety and other factors, to postoperative hostility in cardiac patients. Sequential interviews were conducted before and after surgery. Standardized medical and surgical indices were selected from a national database. Results showed that preoperative spiritual struggle mediated indirect effects of anxiety and anger coping on Interleukin-6 (IL-6) immediately before surgery. The link between spiritual struggle and IL-6 further mediated the indirect effects of anxiety and anger coping on postoperative hostility. Anger coping mediated the harmful influence of anxiety and counteracted the protection of positive religious coping on adjustment.

### Keywords

- *anger*
- *cardiac disease and open-heart surgery*
- *coping*
- *existential stress*
- *hostility*
- *Interleukin-6 (IL-6)*
- *religion and spiritual struggle*
- *stress and mood state*

HOSTILITY and anger have been associated with coronary artery disease (CAD) risk, progression and mortality (Ai, Appel, & Pasic, 2008). Exploring risk and protective factors in this regard may enhance interdisciplinary care and stress management for cardiac surgery patients. Increasingly, research has suggested that faith factors play a key part in coping with chronic conditions through fending off stress effects (Pargament, 1997; Pargament, Murray-Swank, Magyar, & Ano, 2005). Prospective studies suggest that preoperative intrinsic religious factors play a role in recovery from open-heart surgery (e.g. Ai, Park, Huang, Rodgers, & Tice, 2007; Contrada et al., 2004; Oxman, Freeman, & Manheimer, 1995). As yet, however, no study has examined whether maladaptive religious factors and stress biomarkers may jointly accelerate the damaging impact of preoperative distress on postoperative outcomes.

The present study investigated whether negative religious coping (RC) or spiritual struggles (Exline & Rose, 2005; Pargament, Koenig, Tarakeshwar, & Hahn, 2001) and its correlate Interleukin-6 (IL-6), a stress-responsive inflammatory-immune biomarker, may serve as pathways between preoperative distress (as indicated by *anxiety*), and postoperative negative maladjustment (as indicated by *hostility*). Spiritual struggle is centered on deep conflicts in a sacred relationship that may convey significant meaning to an individual's life. Recently, Ai et al. (2007) found that, unlike positive RC, spiritual struggle was predicted by preoperative anxiety, but not by religiousness. Facing a life-altering medical crisis, some people may become more vulnerable to deep existential stress. In these patients, spiritual struggle emerged as a key predictor of preoperative plasma levels of IL-6 (Ai, Seymour, Tice, Kronfol, & Bolling, 2009), suggesting a need for using structural equation modeling (SEM) to test indirect effects of preoperative distress, mediated by the struggle-IL-6 link, on postoperative maladjustment. Several lines of research have lent support for the evaluation of this possible pathway.

First, it has been speculated that religious involvement may benefit health by altering the immune system (George, Ellison, & Larson, 2002; Miller & Thoresen, 2003). Although such involvement is generally linked to improved health (e.g. Koenig, McCullough, & Larson, 2001; McCullough, Hoyt, Larson, Koenig, & Thoresen, 2000), only a few studies have identified negative religious dimensions predicting poorer health (Ai et al., 2007;

Sherman, Simonton, Latif, Spohn, & Tricot, 2005; Zwingmann, Wirtz, Müller, Körber, & Murken, 2006), declines in physical functioning (Fitchett, Rybarczyk, DeMarco, & Nicholas, 1999), or greater mortality among medically ill elderly patients (Pargament et al., 2001). Assessed through the negative religious coping subscale of the RCOPE (Pargament, Koenig, & Perez 2000), spiritual struggle has been consistently associated with higher levels of psychological distress in a meta-analysis (Ano & Vasconcelles, 2005). Trevino et al. (in press) hypothesized that spiritual struggle could influence health outcomes by affecting the immune system. A longitudinal study of 429 HIV/AIDS adults tied baseline spiritual struggle to significant declines in CD4 cells, controlling for demographics and positive religious coping. Conceivably, the struggle-IL-6 link could also predict maladjustment in patients following open-heart surgery.

Second, IL-6, a multi-potent, stress-responsive pro-inflammatory cytokine, plays an important role in CAD and cardiac surgery outcomes (Ai et al., 2008, 2009). There is strong evidence that IL-6 and other pro-inflammatory cytokines are associated with negative affect. Major depressive illness and bipolar disorder have been linked with increased plasma IL-6 (Kiecolt-Glaser et al., 2003; Kim, Jung, Myint, Kim, & Park, 2007; Kronfol & Remick, 2000). Suarez (2003) has used hostility to predict IL-6. Acute inflammation has also been related to negative mood and a transient elevation in IL-6 (Wright, Strike, Brydon, & Steptoe, 2005). Although stressful life events are known to interfere with immunity, the relation between stress and immunity is complex and depends on many variables including the intensity of the stressor, its duration and the context in which it occurs (Brydon, Edwards, Mohamed-Ali, & Steptoe, 2004; Irwin, 2008; Kohut et al., 2006; von Kapel, Kudielka, Preckel, Hanebuth, & Fischer, 2006; Zorrilla et al., 2001). Furthermore, findings on the current stress-inflammation association mostly imply a bidirectional association rather than a definitively single-sided causality. In contrast to the above evidence, one recent study indicated that a mild inflammatory reaction induces a transient negative mood along with an increase in IL-6 (Strike, Wardle, & Steptoe, 2004). Most recently, Marsland, Prather, Petersen, Cohen, and Manuck (2008) associated anger/hostility with IL-6 and C-reactive protein, indicating systematic inflammation, adjusting demographics and health factors. No study has yet investigated the mediation of the

spiritual struggle–IL-6 link in a prospective cardiac study (Ai et al., 2009).

Finally, our earlier report documented the differential antecedents of two uncorrelated forms of RC (Ai et al., 2007). Specifically, religiousness predicted positive RC, but not negative RC, which in turn enhanced hope in these mostly middle-aged and older patients prior to cardiac surgery. By contrast, distress exacerbated spiritual struggle, which in turn led to hopelessness. Likewise, Smith, Pargament, Brant, and Oliver (2000) found the mediation of positive RC, but not that of spiritual struggle, between pre-disaster global religiousness and post-disaster psychological and religious outcomes in flood survivors. The distinct pattern shared by demographically and contextually divergent samples suggests that, under severe stress, the use of positive RC may depend on the firmness of faith. By contrast, the experience of spiritual struggle could be crisis-related or event-specific, manifested as a deep psychological response to existential challenges, regardless of strength in beliefs (Ai et al., 2007). In other words, similar antecedents to different aspects of RC (i.e. positive RC vs spiritual struggle) across crises indicate the potential contrasting nature (i.e. state vs trait) between the two sides: one sustained by a stable belief and the other triggered by distress (Ai et al., 2009). Although the speculation awaits replication in other samples with different beliefs and in different crises, spiritual struggle has been related to other maladaptive coping strategies such as anger coping (Ai et al., 2009). Interestingly, in that report, however, the secular forms of negative coping were not related to IL-6 in the preoperative analysis. These findings imply that spiritual struggle can be a key, universal, but under-explored phenomenon in severe adversity, rather than one for persons of faith per se.

Further research is therefore needed on the struggle–IL-6 pathway in order to improve the interdisciplinary stress management for patients. Based on the literature, the present study constructed a conceptual SEM model, using preoperative factors to predict postoperative outcomes. Earlier reports found that anxiety, reflecting preoperative distress, predicted all maladaptive coping (e.g. anger, spiritual struggle; Ai et al., 2009). Although correlated with each other, these negative styles were differently associated with postoperative hostility, in regression analyses, in which IL-6 also predicted this negative affect (Ai, Kronfol, Bolling, & Tice, under review). Given the complexity, in an SEM estimation, we expected that maladaptive coping

styles could mediate the effects of preoperative stress, indicated by *anxiety*, on postoperative adjustment, indicated by *hostility*.

For hostility, prior multiple regression analyses demonstrated anger coping and spiritual struggle as major predictors, alongside positive RC, but predictive in an opposite direction (Ai et al., under review). Our hypothetical model (Model 1, Fig. 1) thus presented *two maladaptive-coping pathways*, mediated through *anger coping* and the *spiritual struggle–IL-6 link*, respectively, from preoperative *anxiety* to postoperative *hostility*, adjusting key medical predictors (i.e. medical comorbidity, left ventricular ejection fraction (LVEF) and bodily pain) (Ai et al., under review, 2009). Based on the literature (Ai et al., 2007; Smith et al., 2000), positive RC was proposed as *one positive pathway* to mediate religiousness on hostility, counterbalancing undesirable impacts of preoperative distress and illness conditions, in part related to maladaptive coping pathways. We also expected that medical-comorbidity and LVEF, indicating illness severity, would be associated with IL-6, leading in turn to hostility. Furthermore, we anticipated four direct paths from preoperative anxiety and the three illness indicators to hostility, as identified previously (Ai et al., under review).

## Methods

### The sample

The study sample consisted of patients who participated in a psychosocial survey on open-heart surgery at the Heart Center of the University of Michigan Health Systems. Participant eligibility criteria with details were reported (Ai et al., 2009). Attritional analyses found no significant demographic differences (age, gender and race) between consenters who completed the first interview (61 percent of the approached) and nonconsenters. Of all participants, the majority were male (56%), white (91%), and married with spouse present (72%). Average age was 61 years (range, 35–86).

### Procedures

Cardiac surgeons delivered the information package about this study. Nurses screened patients for three sequential interviews on given dates for their preoperative history and physical examination. Around two weeks prior to surgery, trained research assistants (RAs), who were blinded to the cardiac diagnosis and the IL-6 levels of consented patients, conducted the first face-to-face interview for about

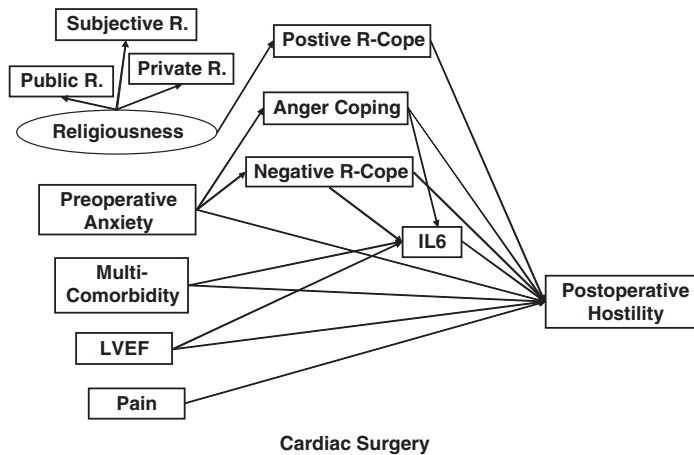


Figure 1. Model 1. Hypothetical model on hostility.

45 minutes at the clinic. This first-wave survey collected the information on preoperative anxiety, medical-comorbidity, bodily pain and religiousness. About two days before operation, patients were contacted for the second 30-minute telephone interview at home. This second-wave survey collected the information on preoperative hope and coping factors. At an average 36 days following operation, patients were contacted for the follow-up. This third-wave survey collected the information on postoperative adjustment. Cardiac and surgical data were retrieved from the Society of Thoracic Surgeon's (STS) database. Peripheral venous blood samples were collected between 8 and 10am. Blood collection procedure and IL-6 assay were detailed previously (Ai et al., 2009).

## Measures

*Medical-comorbidity* was the sum of non-cardiac chronic conditions commonly seen in clinics for middle-aged and older adults (e.g. arthritis, cancer, diabetes;  $M = 2.67$ ,  $SD = 2.12$ ).

*Bodily Pain* was assessed by a five-point scale (1 = None, 5 = Severe;  $M = 2.59$ ,  $SD = 1.23$ ).

*LVEF*, obtained from the STS database, was derived from catheterization and angiography, defined as the percentage of the blood emptied from the ventricle at the end of the cardiac contraction ( $M = 52.72$ ,  $SD = 13.86$ ).

*Preoperative Anxiety* was assessed with the well-validated 20-item, four-point *Trait Anxiety Inventory* (STAI Form X-2; Spielberger, 1988;  $M = 36.84$ ,  $SD = 10.26$ , and Cronbach's  $\alpha/a = .91$ ).

*Religiousness* was measured with the three-factor religiosity scale, including *Public*, *Private*, and *Subjective Religiosity* (Chatters, Levin, & Taylor, 1992). Mean (SD) were 11.51 (4.47), 10.28 (3.80) and 6.05 (1.65), respectively, and  $a$ 's were .86, .76 and .86, respectively.

*Coping Strategies* were assessed with the five-point *Multi-dimensional Coping Scale* (M-Cope; Wills, 1996). The M-Cope assesses four primary dimensions of coping strategies: (a) behavior coping; (b) cognitive coping; (c) anger coping; and (d) avoidant coping. Given the small sample, only the identified predictors for outcomes in previous analyses (c) and (d) (Ai et al., 2009), were included in this modeling, specifically, anger ( $M = 3.45$ ,  $SD = 1.20$ ,  $a = .51$ ) and avoidant ( $M = 4.75$ ,  $SD = 1.65$ ,  $a = .47$ ) coping.

*Religious/Spiritual Coping Styles* were assessed with the four-point *Brief Religious/Spiritual Coping Scale* (Brief RCOPE; Pargament, Smith, Koenig, & Perez, 1998), with seven items each for positive and negative styles. Studies have provided the reliability, concurrent and predictive validity of this measure (e.g. McConnell, Pargament, Ellison, & Flannelly, 2006). Patients responded to these items in terms of how they generally coped with stressors rather than with respect to the operation or heart disease. Positive RC included forgiveness, seeking spiritual support, collaborative religious coping, spiritual connection and benevolent religious reappraisal ( $M = 12.63$ ,  $SD = 6.01$ ,  $a = .93$ ). Negative RC included spiritual discontent, punishing God reappraisals, interpersonal religious discontent, and demonic reappraisal ( $M = 1.20$ ,  $SD = 2.61$ ,  $a = .83$ ).

Indicators of postoperative adjustment, *Hostility*, were assessed with the subscale of the well-validated *Symptom Checklist-90-Revised* (SCL-90-R; Derogatis, 1994;  $M = 7.56$ ,  $SD = 2.15$ ,  $\alpha = .86$ ).

### Statistical analysis

Bivariate correlation analyses were conducted using SPSS-16 to determine univariate associations of constructs in Model 1. Next, the hypothetical model was estimated using SEM, as shown in Model 1. Mean scores of all scaled indicators were used. There was one latent factor, religiousness, with three indicators in Model 1, which predicted positive religious coping earlier (Ai et al., 2008). We evaluated the hypothetical model with the maximum-likelihood estimator and a robust tool, M-PLUS software version 3 (Muthén & Muthén, 1998–2004). In M-PLUS modeling, all structural paths among latent constructs in the hypothetical model are simultaneously estimated, while path coefficients are estimated in the presence of residual measurement errors in the equations. All paths were tested and all direct and indirect effects of the antecedent variables on postoperative hostility were computed in this procedure (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002; Shrout & Bolger, 2002). Nevertheless, the final model displays only statistically significant standardized path coefficients ( $p < .05$ ) in two-tailed tests.

Goodness-of-fit indices, in addition to the chi-square statistics, included the standardized root mean square residual (SMSR) index and the residual mean squared error of approximation (RMSEA) with values around 0.05 (the lower bound of the 90% CI under .05) indicating adequate fit (Bollen & Long, 1993; Browne & Cudeck, 1993), as well as the comparative fit index (CFI) with the recommended adequate fit of values around .90 or greater (Bentler, 1990). Rare missing values were accounted for in listwise deletion.

## Results

### Bivariate correlations

The zero-order correlations of constructs in the final sample of 156 estimated (Model 1) are presented in Table 1. The size of the correlation between paired indicators of one latent factor, religiousness, was at moderately high to high magnitudes (i.e. public, private and subjective religiosity ( $r_s = .77-.90$ ,  $p_s < .001$ )). Signs of significant coefficients were mainly consistent with expected

directions. As seen in Table 1, postoperative hostility was correlated positively with preoperative anxiety, medical-comorbidity, pain, anger coping, negative RC, and IL-6 ( $r_s = .22-.49$ ,  $p_s < .01$  or  $.001$ ), as well as positively with LVEF and negatively with private religiousness at only a modest magnitude. IL-6 was also correlated with subjective religiousness, medical-comorbidity and negative RC ( $r_s = .16-.21$ ,  $p_s < .05$ ), as well as marginally with anger coping. While negative and positive R-cope were not correlated with each other, negative R-cope was additionally correlated with anxiety, pain and anger coping ( $r_s = .19-.35$ ,  $p_s < .05$  or  $.001$ ), whereas positive RC was highly related to the religiousness indicators. Medical-comorbidity was correlated with pain ( $r = .34$ ,  $p < .001$ ), which was also related to private religiousness ( $r = .24$ ,  $p < .01$ ), as well as subjective religiousness at a marginal attitude.

The initial estimation of Model 1 resulted in a satisfactory fit to the data. Yet, the modification index indicated that adding two theoretically plausible paths would improve the model fit. Accordingly, we added the recommended paths (from anger coping to both positive RC and negative RC) to the original Model 1, with no non-significant paths deleted. The final solution is presented in Model 1a (Fig. 2), showing standardized coefficients of all significant paths only, which received no further suggestion for any other path from the modification index. This model demonstrated an adequate measure for one latent factor by respective indicators with high factor loadings. Compared with Model 1, two paths in Model 1a were not significant and thus are not exhibited (i.e. one from negative RC to hostility and one from LVEF to IL-6). The five indices indicated that the model fit the data adequately. The chi-square value was within the acceptable range ( $\chi^2(37, 156) = 58.55$ ). The CFI (.96), TLI (.94), RMSEA (.06, 90%CI .03-.09) and SRMR (.05) were within ranges of appropriate fits. Squared multiple correlations suggest that this model accounted for about 45 percent of the variance in postoperative hostility, 79 percent of that in positive RC, 18 percent of that in negative RC, 6 percent of that in anger coping and 8 percent of that in IL-6.

The significant paths in Model 1a were generally consistent with those in the hypothetical Model 1. Still, not all significant correlations in the zero-order analysis remained a significant path here. Some links should be highlighted. The most noteworthy was the non-significant relationship between negative RC and

Table 1. Correlations of the measured constructs in Model 1 (Postoperative Hostility, N = 156)

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.
1. Post-op Hostility	—										
2. IL-6	.268***	—									
3. Anger Coping	.360***	.149	—								
4. Positive R-cope	-.121	.098	-.031	—							
5. Negative R-cope	.329***	.206**	.325***	-.020	—						
6. Pre-op Anxiety	.489***	.122	.242***	.083	.346***	—					
7. Medical Comorbidity	.215**	.182	.102	.053	.034	.200*	—				
8. Bodily Pain	-.001	.124	.099	.084	.191*	.289***	.336***	—			
9. LVEF	.136	-.078	.058	-.076	-.046	.018	-.036	.060	—		
10. Public R	-.064	.086	.067	.639***	.018	.087	.015	-.003	-.003	—	
11. Subjective R	-.118	.164*	.053	.802***	.059	.069	.018	-.016	-.016	.730***	—
12. Private R	-.153	-.020	.068	.767***	-.053	.115	.087	.064	-.064	.664***	.729***

\*p < .05; \*\*p < .01; \*\*\*p < .001

hostility (path not shown in Model 1a), which in the earlier regression analysis (Ai et al., under review) was significant. Their association was now entirely mediated by IL-6 which also mediated the impact of medical-comorbidity on hostility. Preoperative anxiety was linked with both negative and positive RC, though in opposite directions. The recommended paths indicated the additional influence of distress-related anger coping on both types of RC. LVEF has become a significant predictor for hostility, though its expected impact on IL-6 was not manifest. The three parallel coping-centered paths were presented in this model, while links between medical measures and hostility have been adjusted there. Paths from medical controls show that patients who reported greater medical comorbidity were more likely to experience hostility after their operations, while those who had less bodily pain or better heart function experienced the opposite.

Finally, standardized indirect effects of exogenous variables indicate that, in Model 1a, anxiety had positive indirect effects on postoperative hostility, whereas religiousness presented a significant counteracting indirect effect, chiefly mediated through positive RC. Yet, indirect effects of medical-comorbidity were not significant.

### Discussion

The present study estimated important psychophysiological pathways from preoperative distress, and from other key factors to postoperative maladjustment. To our knowledge, this SEM analysis is the first to demonstrate the significant mediating effect of the spiritual struggle-IL-6 link, alongside that of positive religious coping and other maladaptive coping, in this population. Our model also verifies the following indirect effects. First, spiritual struggle mediates the indirect effect of both anxiety and anger coping on IL-6. Second, anger coping also mediates the influence of anxiety on postoperative hostility. As suggested by the modification index, paths from anger coping to spiritual struggle and positive RC (Model 1a) confirm their indirect effects that are not typically demonstrated in regression analyses. Third, positive RC mediates the role of religiousness on a protective pathway, parallel to maladaptive coping ones. Had this counterbalancing positive pathway not been present, the harmful effects of distress and maladaptive coping could have been more damaging. Taken together, these results are consistent with a few studies pointing to the deteriorating impact of negative faith aspects on

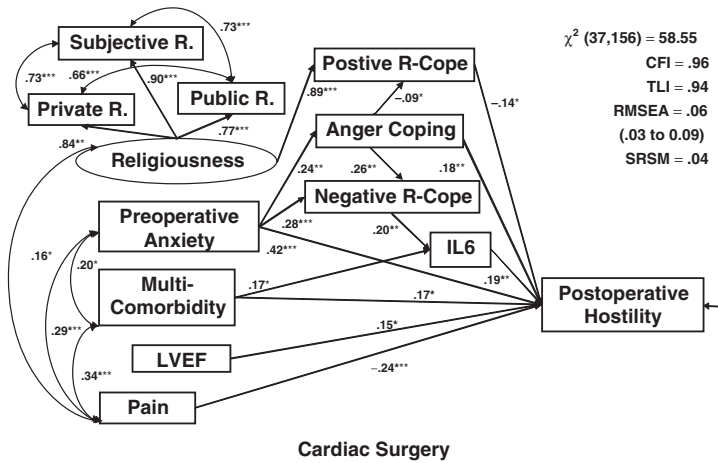


Figure 2. Model 1a. A final conceptual model on hostility.

health outcomes (Ai et al., 2007; Pargament et al., 2001; Sherman et al., 2005; Zwingmann et al., 2006), as well as with research on more positive faith aspects in protecting cardiac surgery patients (Ai et al., 2007; Contrada et al., 2004; Oxman et al., 1995).

This study may provide evidence of a psychophysiological pathway, centering on spiritual struggle, to recovery from a major late-life medical event—open heart surgery. Our study expands the previous finding associating hostility with IL-6 (Suarez, 2003), yet with a reversed prediction, and also draws attention to an important role of spiritual struggle in health. The triangle (anxiety, anger, and struggle) prior to IL-6 suggests that patients who were not only frustrated but also very angry were more likely to undergo spiritual struggle prior to a life-altering operation. Nevertheless, only those who experienced spiritual struggle manifested physiological alteration with respect to excess plasma IL-6. Indeed, it is not stress alone but its existential impact at a deep spiritual level that may trigger an inflammatory response that may influence long-term recovery. A question can arise concerning why anxiety and anger coping were not linked with IL-6 but with spiritual struggle. One possibility is that stress and/or emotions alone could not alter plasma levels of IL-6 (Ellins et al., 2008), but that the intensity of internal conflicts and powerful negative emotions elicited by severe spiritual and existential stress could. Further investigation is needed to develop theories or mechanisms supporting or underlying the complex relationship among biological, psychosocial, and existential factors in health and disease.

Theoretically, this study has some implications for health psychology. It is worth noting that the level of using positive RC was considerably higher than that of pursuing negative RC ( $M_s = 12.63$  vs 1.20). Even so, the lack of influence of religiousness on spiritual struggle as related to anxiety is apparent once again in the final solution (Model 1a), consistent with previous evidence (Ai et al., 2007). This fact indicates that, within this sample, a small subgroup who reported severe spiritual struggle included both religious and non-religious patients who experienced greater preoperative distress. The finding on the struggle-IL-6 link should not be narrowly perceived as a religious phenomenon merely for persons of faith, but as one at a deep existential level across beliefs. Indeed, stress can manifest itself in different ways, such as socio-economical (e.g. financial strain; negative social interaction), psychological (e.g. anxiety associated with traumatic life events), physiological (e.g. alternation of neuroendocrine and immune pathways) and medical (e.g., infection, wound, cancer), as well as spiritual and existential (e.g. religious struggle, existential distress, conflict or suffering). The deeper level of stress should receive more attention among health-stress researchers. Nonetheless, whether spiritual struggle has the same impact on religious and secular persons remains a research question to be tested in the future.

Methodologically, the subsequent analysis presented here demonstrates a certain superiority of using SEM. The advantage of using SEM includes testing the theoretical structure among latent factors with their measurement models (observed variables), demonstrating dependent (endogenous) variables



with measurement errors and confirming multi-level pathways from multiple exogenous variables to outcomes with multiple fit tests (Hoyle, 1995). This analysis reports significant indirect and total effects among constructs, such as the extent to which stress, coping factors and IL-6 may influence one another through multiple or sequential intermediate variables (Bentler, 1990; Bollen, 1993). Therefore, the SEM presence of an indirect stress effect and the absent direct effect of spiritual struggle on postoperative hostility should be seen as more informative regarding mediation than analyses using regression models that would estimate primarily the direct effect of each predictor. Nonetheless, we should also bear in mind that alternative models in SEM are always possible, a fact that underscores the need for a theoretical basis and prospective design for this analytical tool. Also, religiousness, considered as a latent factor, is measured by inter-correlated private, public, and subjective religiosity in the original scale design (Levin, Taylor, & Chatters, 1994). In regression analyses, these components have often been tested as independent predictors, leaving multi-collinearity therein and a role of latent religiousness undetected.

Despite the advantage of testing mediations and pathways for indirect effects, we should also bear in mind the limitations of SEM analyses. Overall, this usage, as with other tools (e.g. regression) for observational data, is not to justify causality, given that no randomized controlled intervention is used to eliminate rival interpretations and/or alternative solutions. Further, SEM is more sensitive to statistical power, and therefore this method limits the number of constructs to be included, despite its advantage for testing mediations in a theoretical model. SEM might not be the best tool for selecting major predictors on their direct effects among numerous candidate independent variables, especially when sample sizes are small in interdisciplinary studies on the progress of major chronic diseases. Rather, it is better performed after initial exploration using regression analyses to identify the direct effects of key determinants.

In addition, the small sample size is a major limitation of this study, though the number of lab assays is relatively large compared with most experimental studies involving biomarkers. The non-experimental design leaves open the possibility of impacts from unexamined confounders on outcomes. Also, findings in a convenience sample might not generalize to other populations, and therefore the findings must be replicated in other populations. This replication is also necessary because the theoretical model was altered

during the course of the analysis. Still, the study was prospectively designed and controlled for key medical factors controlled for. Despite the small sample, a considerable amount of data was generated on each individual, including the biomarker assays. The model indicates the value of SEM in investigating mechanisms (Miller & Thoresen, 2003).

Finally, our earlier analysis indicates that IL-6 was not related to preoperative depression, assessed two weeks earlier, when key medical factors (e.g., LVEF) were controlled for (Ai et al., 2009). Likewise, other confounding variables such as age, smoking, alcohol use, obesity, arthritis, and diabetes commonly seen in psycho-immunological (PNI) research were not predictive either in this cardiac sample. Indeed, as noted by Segerstrom and Miller's meta-analysis (2004) most PNI studies over the past 30 years have primarily used younger, healthier participants, while little research has investigated cardiac patients. In this case, the role of spiritual struggle and IL-6 deserves more attention in the course and treatment of life-threatening and chronic conditions. The outcomes in this study are valuable, though preliminary, given that very little research has investigated psycho-physiological pathways for coping with a highly stressful operation. While numerous studies addressed deteriorating health due to poor social support, our model implies similar health impacts of insecure spiritual support, in relation to an inflammatory biomarker.

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