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Evidence of autonomic dysregulation in otherwise healthy cancer caregivers: A possible link with health hazard

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ABSTRACT

Caregiving, an important component of cancer patient treatment, may set forth a cascade of stress responses such as sympatho-adrenal activation, immuno-humoral changes and an unhealthy lifestyle, which could be hazardous to caregivers' health. In this observational study, we addressed whether autonomic nervous system (ANS) regulation and perception of stress would be altered in a group of 58 health cancer caregivers as compared to 60 controls. We employed non invasive autoregressive spectral analysis of cardiovascular variabilities and ad hoc questionnaires. Caregivers show, in addition to signs of psychological involvement, a clear autonomic imbalance, suggestive of sympathetic predominance at rest and of a reduction of vagal cardiac regulation (overall gain of baroreflex -index α- was respectively of 17.5 ± 1.5 versus 25.1 ± 1.8 msec/mmHg, p<<0.02). These data suggest possible preventive strategies, based on tailored treatments aiming at a betterment of individual autonomic profile.

1. Introduction

Cancer treatment has changed dramatically over the past years, owing to surgical and clinical advances.[1] Consequently, the longer life expectancies and better prognoses impress a stronger importance on the helping relationships of spouses or close relatives; those people that care for the patient.[2]

In general, care giving for a cancer patient falls to the patient's family,[1–3] as a whole, whereby a given member becomes the index caregiver. Caregivers are thus requested not only to dedicate time, energy and emotions to the betterment of the patient's remaining life, but also to maintain a high level of health themselves. Caregiving has been considered 'hazardous to health,[4] because it may set forth a cascade of stress responses such as sympatho-adrenal activation, immuno-humoral changes and an unhealthy lifestyle.[5–7]

Furthermore, the detrimental consequences of caregiving appear quantitatively dependent upon the type and length of disease involved and the closeness of the relationship between caregiver and patient.[1,8] In general, the longer lasting the disease, the older the caregiver and more modest the environmental support, the greater the harmful effect, leading to an increase in mortality risk. In this context attention should also be paid to comorbidities, and in particular to cardiac diseases, an area where stress and autonomic dysfunction play a key role.[9–11]

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The major emphasis of previous studies on caregiving as a risk was mainly on immunological and hormonal changes.[12,13] Very little information is available, to the best of our knowledge, on the role of the autonomic nervous system, whose influence in chronic real life stress can be evaluated with non invasive techniques.[14,15]

Given the close link between stress and autonomic dysregulation, we planned to assess whether stress indicators and indices of autonomic cardiovascular regulation would be altered in caregivers. In particular, we studied a group of cancer caregivers because of the likely greater emotional component and because of the better defined time span of their involvement, as compared with other conditions, such as Alzheimer's, that tend to have a blunted beginning.[1,16,17]

2. Materials and methods

2.1. Study population

This study considers 118 subjects divided into two groups (see Table 1):

A) 58 caregivers (subjects who care daily for a relative with functional limitations, experiencing mental, emotional and physical strain) of cancer patients. They had been caregivers for a median period of 11.5 months (minimum: 1, maximum 139 months).

B) 60 healthy volunteers (controls), who denied any kind of stressful condition as assessed by a semi-structured psychological assessment by a trained investigator.

Subjects of both groups where enrolled in two different locations, a major town in northern Italy: Milan (Oncology Department of L. Sacco Hospital), and a major town in southern Italy: Palermo (Oncology Department of Policlinico Hospital), in order to account for possible cultural bias in the perception of stress.[18]

As in prior studies,[14,15,19] the absence of clinically manifest disease and traditional risk factors in all subjects was determined by history, physical examination, laboratory and routine tests. None of the subjects included in the study were on any medication, nor reported any abuse of alcohol or use of recreational drugs.

Table 1 – Study population

	Caregivers	Controls
N	58	60
Age [yrs]	45.7±1.6	41.4 ± 1.3
Gender (male/female)	28/30	27/33
Body Mass Index [kg/m^2]	24.6 ± 0.5	24.0 ± 0.6
Smokers	11	9
Enrollment location:		
- Milan	30	31
- Palermo	28	29
Caregiving role:		
- husband/wife [%]	38.63 / 18.18	
- son/daughter [%]	11.36 / 22.72	
- sister [%]	6.81	
- friend [%]	2.30	
Cancer:		
- breast [%]	51.61	
- gatrointestinal tract [%]	16.12	
- prostate [%]	12.90	
- lung [%]	12.90	
-linfoma [%]	3.25	
- ovaries [%]	3.22	

2.2. Protocol

Subjects were asked to avoid alcohol and caffeinated beverages for the 12 h preceding the recording session and to abstain from heavy physical activity the day before. All subjects were instructed on the study procedure, and gave their informed consent. Our Institution Ethics Committee approved the protocol of the study.

2.2.1. Stress evaluation

All subjects were assessed by a clinical psychologist through a semi-structured interview in order to establish the possible presence of chronic psychosocial stress, the presence of stress-related symptoms, and to exclude patients with psychiatric diseases (with particular attention to depression and somatoform disorders) following DSM IV criteria.[20]

As in prior studies on the autonomic effects of acute and chronic stress,[14,15,19] all subjects completed a self administered questionnaire providing nominal self-rated scales that focused on overall stress and tiredness perception (I), control (II), stress-related symptoms (III) and quality of life (IV).

(I) Overall Stress and tiredness perception scale: [14,15,19] Likert linear analogue scales from 0 ('no perception') to 10 ('strong perception') were used to approximate the perceived overall stress and tiredness levels.

(II) Control perception was simply assessed using Likert linear analogue scales from 0 ('no control on life events') to 5 ('strong control on life events').

(III) The Subjective Stress-related Somatic Symptoms Questionnaire (4S-Q),[14,15,19] inquired about 18 somatic symptoms accounting for the majority of somatic complaints. For scoring purpose, responses were coded from 0 ('no feeling') to 10 ('a strong feeling'), thus the total score ranged from 0 to 180.

(IV) The SAT-P (Satisfaction Profile).[21] Italian version was employed to assess quality of life. This tool furnishes quality of life data on the following dimensions: psychological, physical, work, sleep, social.

2.2.2. Hormonal evaluation

Hormonal involvement was assessed in a subgroup of 49 (28 caregivers and 21 controls) subjects by measuring, by ELISA assay (DRG, Instruments GmbH, Germany), the Cortisol level in saliva that represents the concentration of the active free Cortisol. Saliva samples (1 mL), from caregivers and controls, were obtained at approximately the same hour (7:30 AM ± 1 h and 10.30 PM ± 1 h) and stored at –20 °C. The time was chosen to accommodate the working routines of all participants.

2.2.3. Autonomic evaluation

After a preliminary 10-min rest period in the supine position, allowing for stabilisation, blood pressure, electrocardiogram (ECG) and respiratory activity were recorded over a 10-min supine baseline and over a subsequent 7-min period of active standing.

To minimise possible emotional bias of the recording procedure, the ECG (CM5) and the respiratory signal were recorded in all subjects with a wireless radiotelemetry system, while an arterial pressure waveform was continuously assessed non-invasively by a Finapres device (Finapres, Ohmeda, Englewood, Colorado, USA). The accuracy of this device in tracking beat by beat blood pressure changes has been previously documented.[22] Data were acquired with a personal computer using an acquisition rate of 300 samples/channel/s.

From the simultaneous autoregressive spectral analysis of RR interval and systolic arterial pressure variability, a series of indexes indirectly reflecting autonomic cardiovascular modulation were derived.[23] RR interval spectral powers were quantified in the low frequency (LF, 0.03 – 0.14 Hz) and high frequency (HF, 0.15 – 0.35 Hz) regions. LF spectral powers were normalised according to the formula $P_{LF[nu]}=[(P_{LF[msec]}{}^{2})/(VAR_{RR[msec]}{}^{2}\text{-}VLF_{[msec]}{}^{2})]*100$ (where $P_{LF[nu]}$=LF powers in the normalised unit, VAR=total variance, VLF=very low frequency component, <0.03 Hz); similar normalisation was performed for HF powers. The LF/HF of RR interval variability power ratio was also computed. According to the sympatho-vagal model, as applied in our laboratory, and on the basis of a strong coherence between similar oscillations in the variability of RR interval and of muscle sympathetic efferent activity,[24] the low frequency component (LF, in normalised units, nu) represents a marker of oscillatory sympathetic modulation of the SA node, while the high frequency component (HF, nu) is a marker of vagal oscillatory modulation.[22–25]

Systolic arterial pressure spectral powers were quantified in the low frequency region (LF, 0.33 – 0.14 Hz) and reported in absolute units, as a marker of sympathetic oscillatory modulation to the vasculature.

The sensitivity of arterial baroreflex control of the RR interval was assessed by the frequency domain α index (average of the square root of the ratio between the RR interval and SB pressure spectral powers in the LF and HF regions).[26]

Monovariate and bivariate spectral analysis of the RR interval variability and respiration were employed to ensure that, in all subjects included in the study, the respiratory rate coincided with the HF component of RR variability and that no respiratory entrainment was present.

2.3. Statistics

Data in the text, figures and tables are presented as means ±standard error. Significance of group differences were assessed with parametric or non parametric tests (Mann–Whitney), with Monte Carlo procedure, as appropriate. Simple non parametric correlation (Spearman) was used to assess the statistical link between stress scores and indices of autonomic cardiovascular regulation. Discriminant analysis was employed to assess the integrated capacity of several psychometric and autonomic variables to correctly classify subjects as controls or caregivers. A p value <0.05 was considered significant. All computations were performed with a commercial statistical package (SPSS 13).

Table 2 – Psychological scores in controls and caregivers

Variables	Stress perception	Tiredness perception	4S-Q	Control perception	Quality of life scores Dimensions				
					Psychological	Physical	Work	Sleep	Social
Controls	4.12 ± 0.36	3.79 ± 0.31	20.16 ± 2.40	3.75 ± 0.15	75.16 ± 2.16	70.88 ± 2.23	60.73 ± 4.43	68.21 ± 2.34	72.81 ± 2.42
Caregivers	6.33 ± 0.30*	6.05 ± 0.31*	36.12 ± 3.33*	3.22 ± 0.13*	67.81 ± 2.23	56.52 ± 1.07*	53.35 ± 4.56	53.52 ± 2.69*	62.31 ± 2.92*

Abbreviation: 4S-Q = Subjective Stress-related Somatic Symptoms Questionnaire.
* Significant differences, p<0.001.

Table 3 – Matrix of nonparametric correlations between psychological scores

		Perception		4S-Q	Perception control	Quality of life scales				
		Stress	Tiredness			Psychol	Physical	Work	Sleep	Social
Perception	Stress	–								
	Tiredness	r=.673 p=.000	–							
	4SQ	r=.618 p=.000	r=.505 p=.000	–						
Perception	Control	r=.214 p=.021	ns	r=.216 p=.021	–					
	Psychol	ns	ns	r=.263 p=.019	r=.522 p=.000	–				
	Physical	r=.309 p=.005	r=.323 p=.003	r=.549 p=.000	r=.301 p=.007	r=.548 p=.000	–			
Quality of life scales	Work	r=.382 p=.001	r=.376 p=.002	r=.391 p=.000	r=.249 p=.042	r=.538 p=.000	ns	–		
	Sleep	r=.464 p=.000	r=.440 p=.000	r=.412 p=.000	r=.360 p=.001	r=.403 p=.000	r=.523 p=.000	ns	–	
	Social	ns	ns	ns	ns	r=.559 p=.000	r=.316 p=.004	r=.398 p=.001	r=.313 p=.004	-

Abbreviation: 4S-Q= Subjective Stress-related Somatic Symptoms Questionnaire.

3. Results

3.1. *Stress evaluation (Table 2)*

Most caregivers reported some form of psychological involvement (feeling of powerlessness, guilt, anger, anticipatory bereavement, somatic symptoms, anxiety, worries for the future, feeling of lack of support, difficulties in handling patients, etc) while none of the control subjects reported any particular source of distress in their life, as per enrolment criteria.

Overall stress and tiredness perception scale: caregivers showed a significantly higher perception of stress and tiredness as compared to controls (respectively 5.63 ± 0.30 versus 4.12 ± 0.36 for stress and 6.05 ± 0.30 versus 3.79 ± 0.31 for tiredness, $p<<0.001$).

Control perception scale: caregivers showed a significantly lower perception of control of life events as compared to controls (respectively 3.22 ± 0.13 versus 3.75 ± 0.15, $p<<0.001$).

Subjective Stress-related Somatic Symptoms Questionnaire (4S-Q): the total 4S-Q score was significantly higher in caregivers as compared to controls (respectively 36.12. ± 3.33 versus 20.16 ± 2.40, $p<<0.001$).

Quality of life: caregivers were characterised by a significantly worse ($p<0.001$) quality of life. This was evidenced by the lower values of physical (56.52 ± 1.07 versus 70.88 ± 2.23), sleep (53.52 ± 2.96 versus 68.21 ± 2.34) and social (62.31 ± 2.92 versus 72.81 ± 2.42) dimension scores as compared to controls. Only non significant differences were found in the psychological and work dimensions comparing caregivers with controls (respectively 67.81 ± 2.23 versus 75.16 ± 2.16 and 53.35 ± 4.56 versus 60.73 ± 4.43).

Table 3 also reports the matrix of significant simple correlations observed between couples of psychological variables.

3.2. *Hormonal evaluation*

No significant differences were observed in salivary cortisol profiles between the two examined groups (morning: controls 22.09 ± 2.00, caregivers 21.31 ± 1.38 ng/ml; night: controls 6.60 ± 1.14, caregivers 8.68 ± 1.13 ng/ml, respectively).

3.3. *Autonomic evaluation (Table 4)*

The resting RR interval and RR interval variance were similar in the two groups.

The LF component of RR interval variability (LF_{RR}), expressed in normalised units (nu) (a marker of sympathetic oscillatory modulation to the SA node), was slightly, but not significantly, higher in caregivers. The HF component of the RR interval variability (HF_{RR}, marker of vagal oscillatory modulation to the SA node), expressed in both absolute and normalised units (nu), was instead significantly lower (Table 4). The LF/HF ratio (a marker of sympatho-vagal balance) was also significantly higher in caregivers.

Systolic arterial pressure, although still in the normal range, was higher ($p< 0.05$) while diastolic pressure was slightly but not significantly greater in caregivers. LF component of SAP variability (LF_{SAP}) was significantly greater ($p<0.02$) in caregivers, while index alpha (a frequency domain marker of the overall gain of baroreflex mechanisms) was significantly ($p<0.002$) lower (see Fig. 1).

Standing induced changes: no significant differences were observed in changes of RR interval, RR variance or absolute values of spectral components between groups; increases in normalised LF (caregivers: 16.3 ± 2.8; controls: 33.8 ± 1.7, in nu) and, reciprocally, reductions in HF (caregivers: -18.1 ± 2.3; controls: -32.5 ± 1.7, in nu) were less evident in caregivers as compared to controls (both, $p<<0.001$). Index alpha showed a significantly ($p<0.05$) smaller reduction with standing in the caregiver group (–7.3 ± 1.4 versus –12.5 ± 1.6 msec/mmHg).

3.4. *Discriminant analysis (Fig. 2)*

To assess the integrated capacity of all employed indices to correctly categorise the study subjects into either caregivers

Table 4 – Descriptive statistics of resting values of RR interval variability in controls and caregivers

Variables	RR	VAR_{RR}	LF_{RR}		HF_{RR}		LF/HF	Respiratory frequency	VAR_{SAP}	LF_{SAP}	α index	SAP	DAP
Units	ms	ms^2	$msec^2$	nu	$msec^2$	nu		Hz	$mmHg^2$	$mmHg^2$	msec/mmHg	mmHg	mmHg
Controls	1057 ± 23	2655 ± 258	840 ± 162	47.5 ± 2.1	773 ± 123	46.3 ± 2.2	1.6 ± 0.2	0.23 ± 0.0	22.2 ± 4.2	2.6 ± 0.4	25.1 ± 1.8	118 ± 2	74 ± 1
Caregivers	1101 ± 27	2200 ± 257	598 ± 120	53.4 ± 2.8	444 ± 79*	37.6 ± 2.8*	2.9 ± 0.5*	0.24 ± 0.0	23.9 ± 4.9	4.9 ± 0.9*	17.5 ± 1.5*	124 ± 2**	77 ± 1

Abbreviations: RR= RR interval, VAR_{RR} =RR variance, LF_{RR} = low frequency component of RR interval variability, HF_{RR}= high frequency component of RR interval variability, LF/HF= ratio between low and high frequency components, VAR_{SAP} =SAP variance, LF_{SAP} = low frequency component of SAP interval variability, SAP=systolic arterial pressure, DAP= diastolic arterial pressure. nu= normalised units. Significant differences: *p<0.02; **p<0.05.

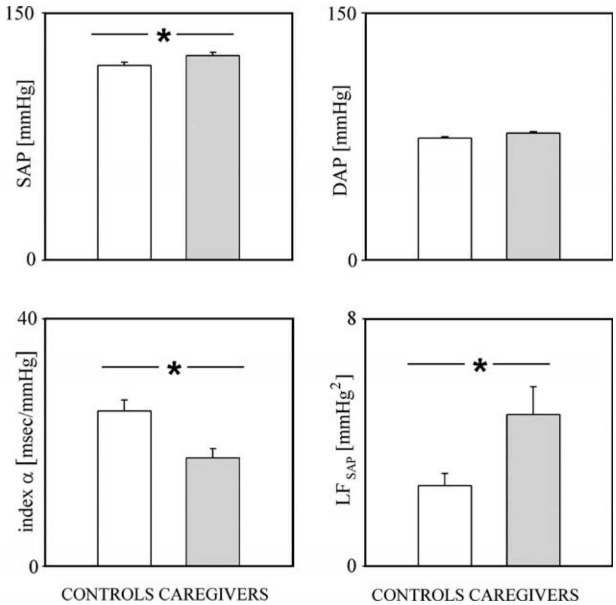

Fig. 1 – Average value (and SEM) of systolic (SAP, left top panel), and diastolic arterial pressure (DAP, right top panel) at rest, and of overall gain of baroreflex (index α, left bottom panel) and of the marker of the sympathetic modulation to the vasculature (LF_{SAP}, right bottom panel) in controls (white bars) as compared to caregivers (grey bars). * p< 0.02.

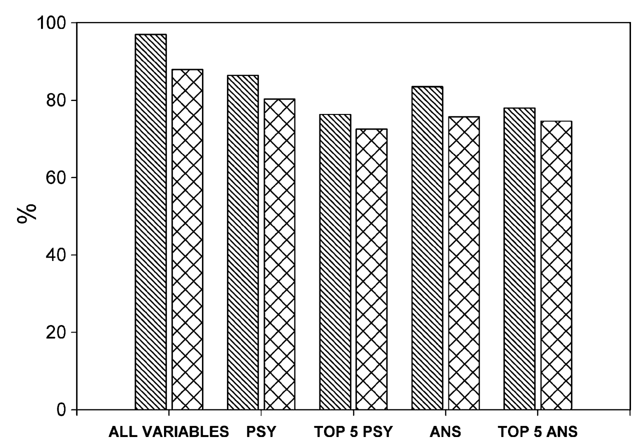

Fig. 2 – Discriminant analysis showing the high classification power of interested variables, and the modest loss of classification power produced by progressively restricting the number of variables employed in the model. Notice that even using only the five top ranking variables (both for psychological -PSY- and autonomic –ANS- variables) the correct classification is still higher than 70%, suggesting that these variables capture a large fraction of the information necessary to correctly allocate subjects to either controls or patients. Lined bars: original cases; Crossed bars: cross-validated cases.

or controls, discriminant analysis was also performed. While the combination of both psychological and autonomic variables provided a correct classification in about 90% of cases, the separate use of all psychometric or autonomic variables slightly reduced correct classification to ≈ 80%. Notably, further restricting the number of all variables to the top ranking 5 determined an additional small loss of classification capacity that remained higher than 70%.

4. Discussion

In this observational study we report that cancer caregivers show, in addition to signs of psychological involvement, a clear autonomic imbalance, suggestive of sympathetic predominance at rest and of a reduction of vagal cardiac regulation.

4.1. *Caregiving and psychological involvement*

In our investigation, caregivers for close relatives affected by cancer consistently demonstrated elevated values of self reported markers of psychological involvement,[1–3,27] and reduced quality of life. This was of no surprise, and in line with several recent studies, shows that caring for a close relative may be dangerous for the health and well being of the caregiver, up to the point of increasing the risk of mortality.[4,5] What might merit further thinking is the technique that we employed to assess psychological aspects. [14,15,19] Indeed, we combined two approaches. As usual in our laboratory, a simple technique based on Likert scales was employed to focus on the domains of stress and bodily symptoms. With this approach we have shown that real life stress induces profound changes in bodily perception,[14,15,19,28] in absence of any evidence of organ malfunction or disease, and that these symptoms may predict cardiovascular dysregulation,[14,15,19] such as increases in arterial pressure in patients, or reduced performance in elite athletes.[28] In this study, as is customary in the field of caregiving, we also assessed quality of life, and found reduced values for physical, sleep and social dimensions. Notably, a strong correlation was observed between indices of stress and quality of life (Table 3), supporting their complementary rather than alternative value.

4.2. *Autonomic imbalance*

Our study provides new information on the selective role of different autonomic oscillatory mechanisms in cancer caregivers using markers derived from autoregressive spectral analysis of cardiovascular variabilities. With this technique, increases in sympathetic modulation to the sino atrial node are signalled by a relative increase in the normalised power of the LF component as it occurs with upright posture in normal individuals or with essential hypertension.[23–25] Cardiac vagal modulation is gleaned by the relative power of the high frequency component (HF) and by its changes with the upright posture, by the absolute value of RR variability, as well as by the gain of the baroreflex (index alpha).[22–26]

In caregivers we observed a profile of autonomic indices suggestive of initial cardiovascular dysregulation. In fact, cardiac vagal withdrawal at rest was suggested by a diminished value of the alpha index of baroreflex gain, combined with a reduced normalised power of the HF component of RR variability. Cardiac and vascular sympathetic activation were suggested by, respectively, an increase in the LF/HF ratio and by an increase in the LF power of SAP variability. As is customary in our laboratory, autonomic cardiovascular regulation was assessed not only at rest but also in response to an excitatory stimulus, produced by active standing.[22–26] A diminished autonomic responsiveness to standing up was clearly evidenced by a lesser increase of LF_{RR} (and the mirror decrease of HF_{RR} and of the index alpha).

Caregivers also demonstrated an increase of the LF power of systolic arterial pressure variability, suggesting an increase of sympathetic vascular drive.[26] Although the evaluation of molecular or genetic underpinning of these changes was not an aim of this investigation, it may be recalled that chronic stress is capable of increasing the LF component of SAP variability, possibly as a reflection of impaired endothelial function.[29,30]

4.3. *Limitations of the study*

This is a preliminary observational study based on a single time point, relatively close to the beginning of care giving (median time 11.5 months) and thus we could not describe a time course of changes. Moreover, we could not observe extremes of effects, as it might happen in other conditions, such as the longer lasting caregiving of Alzheimer patients, which could induce more apparent changes. In this sense we report no change in salivary cortisol, a well known indicator of high stress. In the model proposed by Grant,[4] this would thus imply that patients of the present study are still in an initial phase, limited to autonomic activation.

A second limitation of the study regards the relatively small group of caregivers that were, however, carefully selected without any evidence of clinical or subclinical disease, which would have clouded any autonomic observation.

4.4. *Clinical implications*

Caregiving is not only linked to a reduced quality of life, but also to an increased morbidity or mortality risk: [4,5] the results of our study might provide suggestions for mechanisms and possible treatments on this ominous relationship.

Caregivers, in addition to the obvious emotional and physical burden,[1–3] and having less time to look after oneself, are exposed to an array of stressors and to negative lifestyles, ranging from lack of rest, isolation and reduction of social support, to changes in nutrition, smoking habits, alcohol and drug abuse, together with a lack of exercise.[1–4,6,27]

The increased risk observed in caregivers, particularly in the cardiovascular area,[4,5] may thus not only be due to indirect mechanisms initiated by these behavioral changes, but also to the negative mechanistic influence of autonomic dysregulation, and in particular, the observed reduction of baroreflex gain. This hypothesis is not only relevant to mechanistic considerations, but, as in other conditions of stress,[15,31] would open the way to possible lifestyle change strategies, which have been shown to be capable of improving and preventing impairment of autonomic profile.

Conflict of interest statement

None declared.

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REFERENCES

1. Kim Y, Schulz R, Carver CS. Benefit-finding in the cancer caregiving experience. *Psychosom Med* 2007;**69**:283–91.
2. Rolland JS. Cancer and the family. *Cancer* 2005;**104**:2584–95.
3. Christakis NA, Iwashyna TJ. The health impact of health care on families: a matched cohort study of hospice use by decedents and mortality outcomes in surviving, widowed spouses. *Soc Sci Med* 2003;**57**:465–75.
4. Grant I. Caregiving may be hazardous to your health. *Psychosomatic Medicine* 1999;**61**:420–3.
5. Schultz RBS. Caregiving as a risk factor for mortality - The caregiver health effects study. *JAMA* 1999;**282**:2215–9.
6. Schulz R, Newsom J, Mittelmark M, Burton L, Hirsch C, Jackson S. Health effects of caregiving: the caregiver health effects study: an ancillary study of the Cardiovascular Health Study. *Ann Behav Med* 1997;**19**:110–6.
7. Shaw WS, Patterson TL, Ziegler MG, Dimsdale JE, Semple SJ, Grant I. Accelerated risk of hypertensive blood pressure recordings among Alzheimer caregivers. *J Psychosom Res* 1999;**46**:215–27.
8. Vedhara K, Shanks N, Anderson S, Lightman S. The role of stressors and psychosocial variables in the stress process: a study of chronic caregiver stress. *Psychosom Med* 2000;**62**:374–85.
9. Rozanski A, Blumenthal JA, Saab PG, Davidson KW, Kubzanski L. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice. the emerging field of behavioural cardiology. *JACC* 2005;**45**:637–51.
10. Pagani M, Lucini D. Cardiovascular physiology, emotions, and clinical applications: are we ready. Am J Physiol Heart Circ Physiol 2008.
11. Curtis BM, O'Keefe Jr JH. Autonomic tone as a cardiovascular risk factor: the dangers of chronic fight or flight. *Mayo Clin Proc* 2002;**77**:45–54.
12. Ranjit N, Young EA, Kaplan GA. Material hardship alters the diurnal rhythm of salivary cortisol. *Int J Epidemiol* 2005;**34**:1138–43.
13. Li J, Cowden LG, King JD, et al. Effects of chronic stress and interleukin-10 gene polymorphisms on antibody response to tetanus vaccine in family caregivers of patients with Alzheimer's disease. *Psychosom Med* 2007;**69**:551–9.
14. Lucini D, Norbiato G, Clerici M, Pagani M. Hemodynamic and Autonomic Adjustments to Real Life Stress Conditions in Humans. *Hypertension* 2002;**39**:184–8.
15. Lucini D, Riva S, Pizzinelli P, Pagani M. Stress management at the worksite: reversal of symptoms profile and cardiovascular dysregulation. *Hypertension* 2007;**49**:291–7.
16. Clipp EC, George LK. Dementia and cancer: a comparison of spouse caregivers. *Gerontologist* 1993;**33**:534–41.
17. BM StetzKM. Physical and psychological health in family caregiving: a comparison of AIDS and Cancer caregivers. *Public Health Nursing* 2004;**21**:533–40.
18. Rosengren A, Hawken S, Ôunpuu S, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 case and 13648 controls from 52 countries (The INTERHEART study): case control study. *Lancet* 2004;**364**:953–62.
19. Lucini D, Di Fede G, Parati G, Pagani M. Impact of chronic psychosocial stress on autonomic cardiovascular regulation in otherwise healthy subjects. *Hypertension* 2005;**46**:1201–6.
20. (1994) Diagnostic and Statistical Manual of Mental Disorders IV (DSMIV). American Psychiatric Society, Washington, DC.
21. Majani G, Callegari S. Test SAT-P - Soddisfazione soggettiva e qualita' della vita. Edizioni Erickson edn. 2008.
22. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. *Circulation* 1991;**84**:482–92.
23. Pagani M, Lombardi F, Guzzetti S, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympathovagal interaction in man and conscious dog. *Circ Res* 1986;**58**:178–93.
24. Pagani M, Montano N, Porta A, et al. Relationship between spectral components of cardiovascular variabilities and direct measures of muscle sympathetic nerve activity in humans. *Circulation* 1997;**95**:1441–8.
25. Lucini D, Mela GS, Malliani A, Pagani M. Impairment in cardiac autonomic regulation preceding arterial hypertension in humans. *Insights from spectral analysis of beat-by-beat cardiovascular variability. Circulation* 2002;**106**:2673–9.
26. Pagani M, Somers VK, Furlan R, et al. Changes in autonomic regulation induced by physical training in mild hypertension. *Hypertension* 1988;**12**:600–10.
27. Kim Y, Duberstein PR, Sorensen S, Larson MR. Levels of depressive symptoms in spouses of people with lung cancer: effects of personality, social support, and caregiving burden. *Psychosomatics* 2005;**46**:123–30.
28. Iellamo F, Pigozzi F, Spataro A, et al. Autonomic and psychological adaptations in Olympic rowers. *J Sports Med Phys Fitness* 2006;**46**:598–604.
29. Ghiandoni L, Donald AE, Cropley M, et al. Mental stress induces transient endothelial dysfunction in humans. *Circulation* 2000;**102**:2473–8.
30. Iellamo F, Tesauro M, Rizza S, et al. Concomitant impairment in endothelial function and neural cardiovascular regulation in offspring of type 2 diabetic subjects. *Hypertension* 2006;**48**:418–23.
31. Milani RV, Lavie CJ. Stopping stress at its origins. *Hypertension* 2007;**49**:268–9.