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## Increased blood pressure reactions to acute mental stress are associated with 16-year cardiovascular disease mortality

Running head: Stress reactivity and cardiovascular disease mortality

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## **Abstract**

Exaggerated cardiovascular reactions to acute psychological stress may be involved in the aetiology of cardiovascular pathology. The present analysis examined the association between the magnitude of systolic and diastolic blood pressure reactions to stress and cardiovascular disease mortality. Participants were 431 (229 women) from the West of Scotland Twenty-07 Study, aged 63 years at the time of stress testing, where blood pressure was measured during resting baseline and mental arithmetic stress. Participants' vital status was tracked for the next 16 years, during which time 38 had died of cardiovascular disease. Both systolic and diastolic blood pressure reactions were positively associated with cardiovascular disease mortality. This association could reflect the long term erosive effects of exaggerated reactivity on the vasculature as well as its short term capacity to trigger acute cardiovascular events.

**Descriptors:** Cardiovascular disease mortality, Systolic blood pressure, Diastolic blood pressure, Cardiovascular Reactivity, Acute stress.

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The reactivity hypothesis posits that large magnitude cardiovascular reactions to acute psychological stress play a role in the development of cardiovascular pathology (Light, 1981; Manuck, Kasprovicz, & Muldoon, 1990; Obrist, 1981). The hypothesis has proved to be both influential and durable (Turner, 1994; Wright & Gendolla, 2011). It is certainly the case that the cardiovascular adjustments observed during acute psychological stress differ from those that occur during physical exertion in that the latter are closely coupled with the metabolic demands of motor behaviour whereas the former are apparently uncoupled from the energy demands of behaviour and might be properly regarded as metabolically exaggerated. For example, in two recent studies in our laboratory we measured cardiovascular activity and oxygen consumption during acute stress exposure and graded sub-maximal cycling. The individual oxygen consumption-cardiovascular activity regression equations calculated for graded exercise allowed us to predict what cardiovascular activity should have been during stress given contemporary levels of oxygen consumption. The recorded levels of stress-related cardiovascular activity were well in excess of what was predicted (Balanos et al., 2010; Carroll, Phillips, & Balanos, 2009). Thus, it is easy to see why, in contrast to the biologically appropriate and health enhancing adjustments during physical activity, large magnitude cardiovascular reactions to psychological stress might be considered pathophysiological.

More direct evidence in support of the reactivity hypothesis comes from a number of large scale cross-sectional and prospective observational studies that attest to positive associations between the magnitude of cardiovascular reactions to acute psychological stress tasks and future blood pressure status and hypertension (Carroll, Phillips, Der, Hunt, & Benzeval, 2011; Carroll, Ring, Hunt, Ford, & Macintyre, 2003; Carroll, Smith, Sheffield, Shipley, & Marmot, 1995; Carroll et al., 2001; Markovitz, Raczynski, Wallace, Chettur, & Chesney, 1998; Matthews,

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Woodall, & Allen, 1993; Newman, McGarvey, & Steele, 1999), markers of systemic atherosclerosis (Barnett, Spence, Manuck, & Jennings, 1997; Everson et al., 1997; Lynch, Everson, Kaplan, Salonen, & Salonen, 1998; Matthews et al., 1998), and left ventricular mass and/or hypertrophy of the heart (Georgiades, Lemne, de Faire, Lindvall, & Fredrikson, 1997; Kapuku et al., 1999; Murdison et al., 1998). The effect sizes are generally small but the evidence is certainly consistent with the main tenets of the reactivity hypothesis. A recent meta-analysis of 36 studies confirms this conclusion; the authors report an aggregate  $r = .091$ ,  $p < .001$ , which connotes a small but highly significant effect (Chida & Steptoe, 2010).

No study to date, however, has examined the association between cardiovascular stress reactions and cardiovascular disease (CVD) mortality. Data from the West of Scotland Twenty – 07 Study affords just such an analyses; the eldest of the three age cohorts was *circa* 63 years old at the time of stress testing and their mortality status has been tracked for the subsequent 16 years. On the basis of the reactivity hypothesis, we anticipated a positive association between the magnitude of blood pressure reactions to acute stress and subsequent risk of CVD death.

## **Method**

### **Participants**

Data analyses focused on the eldest of the three discrete age cohorts that comprise the West of Scotland Twenty – 07 Study (Benzeval et al., 2009). Participants were all from the Glasgow area and have been surveyed periodically since 1988. They were virtually all Caucasian, commensurate with the area's demographics. The West of Scotland Study's principal aim was to

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investigate the processes that generate and maintain socio inequalities in health (Macintyre, 1987). Participants were chosen randomly with probability proportional to the overall population of the same age within selected postal code areas based on a stratified sample of postal codes (Ecob, 1987). The present analysis is based on the third wave of data collection and the effective sample size was 431 (229 women). At the time of cardiovascular stress testing in 1995/96, participants were all around 63 years old: mean (SD) age was 63.57 (0.61). The study was approved by the appropriate ethics committees, conducted in accord with the Declaration of Helsinki, and all participants provided informed consent.

## **Procedure**

Testing sessions were conducted by trained nurses in a quiet room in the participants' homes.

Demographic and other information was obtained by questionnaire. Household socioeconomic status (SES) was characterized as manual or non-manual from the occupation (or final occupation, if retired) of the head of household, using the Registrar General's classification system (OPCS, 1980). From questions on smoking behavior, participants were classified as never, ex, or current smokers. Long-standing, chronic illness status was determined by the question, 'Do you have any long-standing illness, disability or infirmity? By long-standing I mean anything that has troubled you over a period of time or that is likely to affect you over a period of time.' From a raft of questions on physical activity a summary measure of whether or not participants met the then recommended guidelines of five moderate or three strenuous bouts of activity per week was derived. Height and weight were measured and body mass index (BMI) computed.

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The acute stress task was the paced auditory serial arithmetic test (PASAT), which has been shown in numerous studies to reliably perturb the cardiovascular system (Ring, Burns, & Carroll, 2002; Winzer et al., 1999), and to demonstrate good test-retest reliability (Willemsen et al., 1998). The nurses were all trained in administering the PASAT by the same trainer and followed a written protocol. The test comprised a series of single digit numbers presented by audiotape. Participants were required to add sequential number pairs, while at the same time retaining the second of the pair in memory to add to the next number presented. Answers were given orally and the correctness of the answers recorded as a measure of performance. The first sequence of 30 numbers was presented at a rate of one every 4 seconds, and the second at one every 2 seconds. In all, the task lasted 3 minutes. Only those who registered a score on the PASAT were included in the analyses. Of a possible score of 60, the mean (SD) score was 40.86 (9.03).

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded using a brachial cuff and a semi-automatic sphygmomanometer (model 705CP, Omron, Weymouth, UK). This blood pressure measuring device is recommended by the European Society of Hypertension (O'Brien, Waeber, Parati, Staessen, & Myers, 2001). After questionnaire completion (taking at least an hour), there was a formal 5-minute period of relaxed sitting, at the end of which a resting baseline reading was taken. Task instructions were then given and participants allowed a brief practice to ensure they understood the requirements of the PASAT. Two further blood pressure readings were then taken, the first initiated 20 seconds into the task (during the slower sequence of numbers) and the second initiated 110 seconds later (during the faster sequence of numbers). The two task readings were averaged and the resting baseline value subtracted, to yield reactivity measures for SBP and DBP.



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Vital status was then continuously monitored. The end point of monitoring for the present analyses was 7<sup>th</sup> November, 2011, i.e., 16 years after the cardiovascular stress testing exposure.

The study participants were flagged using the UK's National Health Service Central Registry, which provided notification of death as well as cause of death. Mortality due to CVD was classified using the International Classification of Diseases (ICD) (21) codes: ICD-9: 390–434, 436–448, and ICD-10: I00–I78 which comprised: acute rheumatic fever; chronic rheumatic heart diseases; hypertensive diseases; ischaemic heart diseases; pulmonary heart disease and diseases of pulmonary circulation; other forms of heart disease; cerebrovascular diseases; diseases of arteries, arterioles and capillaries.

### **Data analyses**

Differences between those who had and had not died from CVD on the various covariates were compared using  $\chi^2$  (categorical data) and ANOVA (continuous data). Average SBP and DBP levels during the stress tests were compared to baseline values using repeated measures ANOVA. SBP and DBP stress reactivity were then computed as the average task value minus the baseline. For the ANOVAs partial  $\eta^2$  is reported as a measure of effect size. Cox's proportional hazard models were used to analyze the CVD mortality data. First, we examined the association between blood pressure stress reactivity and CVD mortality in unadjusted models. Second, we tested models that adjusted for age, sex, SES, smoking, BMI, physical activity, long-standing chronic illness, baseline blood pressure, and antihypertensive medication. Finally, analogous analyses were undertaken for all cause mortality.

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## Results

Thirty eight participants had died from CVD during the 16 years subsequent to stress testing. The key characteristics of those who had and had not died of CVD are summarized in Table 1. Current smokers, those from manual socioeconomic households, those who were physically inactive, and those with long-standing illness were more likely to have died of CVD. Men were more likely than women to have died of CVD, but this effect did not meet the conventional criterion of statistical significance. The stress task perturbed both SBP,  $F(1, 430) = 261.94, p < .001, \eta^2 = .379$ , and DBP,  $F(1, 430) = 338.03, p < .001, \eta^2 = .440$ ; the summary statistics are presented in Table 2.

Unadjusted hazard models revealed positive, but non-significant, associations between SBP stress reactivity,  $HR = 1.019, 95\%CI 0.995 - 1.044, p = .12$ , and DBP stress reactivity,  $HR = 1.029, 95\%CI 0.994 - 1.066, p = .10$ , and CVD mortality. However, in models that adjusted for age, sex, SES, smoking, BMI, physical activity, long-standing chronic illness, baseline blood pressure, and antihypertensive medication, these positive associations were statistically significant for both SBP reactivity,  $HR = 1.032, 95\%CI 1.003 - 1.062, p = .03$ , and DBP reactivity,  $HR = 1.049, 95\%CI 1.003 - 1.096, p = .04$ . The main variables whose absence appeared to suppress the association between blood pressure reactivity and CVD mortality were: long-standing illness, SES, and physical activity. In models that adjusted only for these three variables the strength of the association between reactivity and CVD mortality was of the same

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order as that evident in the fully adjusted models: HR = 1.030, 95%CI 1.004 – 1.057,  $p = .03$ , and HR = 1.044, 95%CI 1.005 – 1.086,  $p = .03$ , for SBP and DBP reactivity respectively. In the fully adjusted models, then, for every one standard deviation increase in SBP and DBP stress reactivity there was a 3% and 5% increase, respectively, in the likelihood of having died of CVD during the 16 years of monitoring. The relevant survival curves based on these adjusted models are displayed in Figures 1 and 2, for SBP and DBP stress reactivity respectively. These contrast participants in the top quartiles of SBP and DBP stress reactivity with the rest of the sample. Finally, SBP and DBP reactivity were not significantly associated with all cause mortality risk in either unadjusted, HR = 0.999, 95%CI 0.987 – 1.011,  $p = .87$  and HR = 1.012, 95%CI 0.995 – 1.029,  $p = .16$ , respectively, or fully adjusted models, HR = 1.002, 95%CI 0.989 – 1.016,  $p = .74$  and HR = 1.016, 95%CI 0.996 – 1.037,  $p = .12$ , respectively.

## Discussion

In multivariate Cox's proportional hazard models, adjusting for age, sex, socioeconomic status, smoking, body mass index, physical activity, long-standing chronic illness, and resting blood pressure, exaggerated SBP and DBP reactions to an acute psychological stress task were associated with an increase in the risk of CVD, but not all-cause, mortality, over the subsequent 16 years. This finding extends previous observations linking cardiovascular stress reactivity to future blood pressure status (Carroll, et al., 2003; Carroll, et al., 1995; Carroll, et al., 2001; Markovitz, et al., 1998; Matthews, et al., 1993; Newman, et al., 1999), markers of systemic

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atherosclerosis (Barnett, et al., 1997; Everson, et al., 1997; Lynch, et al., 1998; Matthews, et al., 1998), and left ventricular mass and/or hypertrophy of the heart (Georgiades, et al., 1997; Kapuku, et al., 1999; Murdison, et al., 1998). It also offers unique support to the reactivity hypothesis which contends that, over the life course, exaggerated cardiovascular reactions to acute stress exposures play a role in the development of cardiovascular pathology. That the associations are evident in multivariate analyses but are not statistically significant in univariate analyses might be regarded as curious. However, given that so many other factors contribute to CVD mortality (in our analyses, smoking, physical inactivity, long-standing illness, and low SES were all highly predictive), we would contend the univariate model is sub-optimal and that only multivariate models afford a proper test of our original hypothesis. Indeed, in models entering, in addition to reactivity, only physical activity, SES, and illness, both SBP and DBP reactivity were as strongly predictive of CVD mortality as they were in our fully adjusted models.

It is unclear what the mechanisms are that link exaggerated blood pressure stress reactivity to future CVD mortality. There are at least two possible routes. First, evidence indicates (see above) that exaggerated pressor responses across the life course are associated prospectively with the preconditions for CVD mortality: hypertension and atherosclerosis. Whereas we were able to adjust for resting blood pressure and antihypertensive medication in the present study, we have no data on concurrent arterial stenosis. Second, acute stress exposure has been implicated in triggering acute CVD events (Tofler et al., 1990). Earthquakes, missile attacks, and even key sporting events have all been linked to increased hospital admissions for and/or mortality from CVD (Bergovec et al., 1992; Carroll, Ebrahim, Tilling, Macleod, & Smith, 2002; Leor & Kloner, 1996; Meisel et al., 1991; Trichopoulos, Katsouyanni, Zavitsanos, Tzonou, & Dalla-Vorgia, 1983; Witte, Bots, Hoes, & Grobbee, 2000). Laboratory stress exposures that increase blood

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pressure also increase haematocrit and blood viscosity, and reduce coagulation time (de Boer et al., 2007) creating what might be regarded as a prothrombic state. Indeed, the evidence suggests that such rheological changes are mediated by the arterial pressure stress response (de Boer, et al., 2007). Accordingly, exaggerated blood pressure stress reactivity may be accompanied by greater prothrombic changes.

The present study is not without limitations. First, the sample size is modest and there were only 38 CVD deaths. However, the study had sufficient power to detect significant associations between stress reactivity and CVD mortality. Second, the effects sizes are small. However, they are of the same order as or larger than those we reported previously from this study for cardiovascular reactivity and the upward drift of blood pressure over time and hypertension (Carroll, et al., 2011; Carroll, et al., 2003). Further, although, in advance of replication, it would be premature to speculate on the health implications of our findings, it is perhaps worth pointing out that at an individual level the risk of dying from CVD associated with high blood pressure reactivity was greater than that associated with high BMI in the present study. Third, the present sample was relatively older than those in the majority of the prospective studies of stress reactivity and this may limit generalization. However, two previous studies of reactivity and cardiovascular outcomes stress tested samples that were in their mid to late 50s (Lynch et al., 1998; Matthews et al., 1998). Further, it is almost inevitable in a study of CVD mortality that the sample will be older at entry; otherwise, there would be insufficient events to analyze in a realistic time frame. Fourth, observational studies, even prospective ones, cannot definitively determine causality. There is always the issue of confounding by some unmeasured or poorly measured variable {Christenfeld, 2004 #524}. However, we did adjust statistically for many potential confounders. Finally, the reliance on self-report for important health-related measures

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such as smoking and long-standing illness might also be regarded as a weakness. However, the concordance in reported smoking status between adjacent surveys in this study exceeded 90% and self-reported smoking behaviour correlates strongly with cotinine and other biochemical measures of smoking (Woodward, Moohan, & Tunstall-Pedoe, 1999). In addition, the methodology used to ascertain long-standing illness has shown little bias in reporting (Macintyre, 1987).

In conclusion, individuals who show large magnitude SBP and DBP reactions to acute psychological stress are at increased risk of subsequently dying from CVD. This finding adds support to the hypothesis that exaggerated stress reactivity plays a role in cardiovascular pathology, through its long term erosive effects on the vasculature and/or by serving as a short term prothrombic trigger for acute cardiovascular events.

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Table 1. Characteristics of those who had and had not died of cardiovascular disease

		Died of CVD (N = 38)	Did not die of CVD (N = 393)	
		M (SD)	M (SD)	<i>p</i>
Age		63.51 (0.62)	63.58 (0.64)	.49
Body mass index		25.35 (4.46)	26.39 (4.28)	.16
		N (%)	N (%)	
Sex	Male	23 (61)	179 (46)	.08
	Female	15 (39)	214 (54)	
Socioeconomic status	Manual	29 (76)	207 (53)	.006
	Non-manual	9 (24)	183 (46)	
Smoking	Never	5 (13)	150 (38)	.005
	Ex	14 (37)	126 (32)	
	Current	19 (50)	117 (30)	
Met activity criterion	Yes	3 (8)	110 (28)	.01
	No	33 (92)	281 (72)	
Long-standing illness	Yes	10 (26)	37 (9)	.001
	No	28 (74)	356 (91)	

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Table 2. Systolic and diastolic blood pressure levels at baseline and during the stress task.

	Baseline	Stress task	
	M (SD)	M (SD)	<i>p</i>
Systolic blood pressure	144.35 (21.67)	156.68 (22.80)	< .001
Diastolic blood pressure	83.83 (11.17)	90.79 (13.23)	< .001

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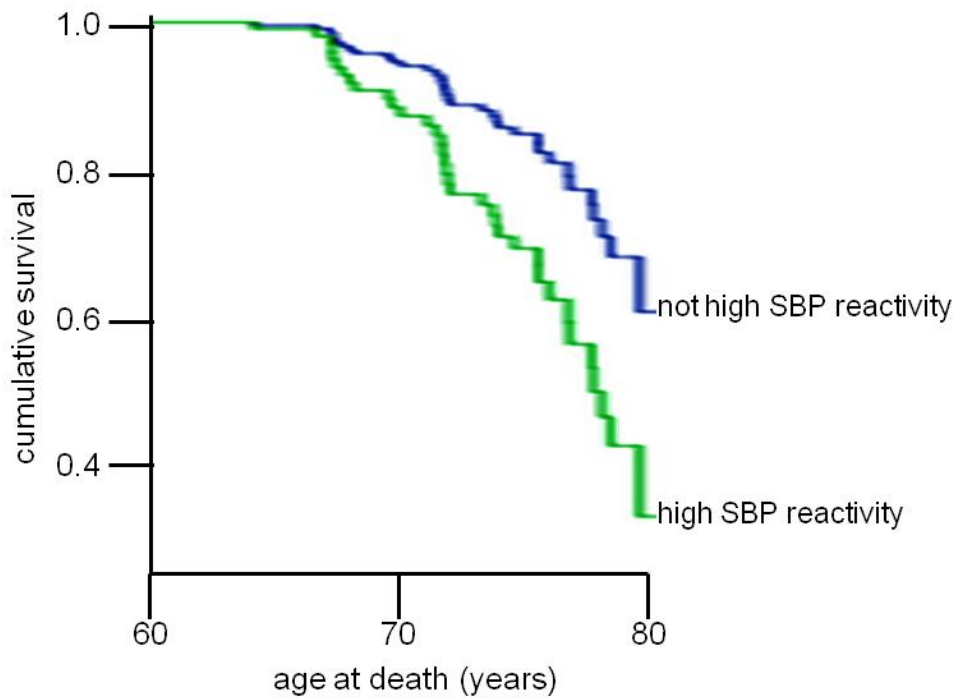
Figure Captions:

Figure 1. CVD mortality survival curves for participants in the top quartile of SBP reactors versus the rest of the sample

Figure 2. CVD mortality survival curves for participants in the top quartile of DBP reactors versus the rest of the sample



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