Effects of stress on brachial artery flow mediated vasodilatation in doctors after a 24-hour-duty

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ABSTRACT

Introduction: Psychosocial stress including work-related stress has been shown to cause endothelial dysfunction and plays a role in the aetiology and pathogenesis of a wide range of cardiovascular diseases. Junior doctors are exposed to high levels of daily work-related stress and more so when they are on-call. This study aimed to investigate the adverse effects of stress of being on-call for 24-hours on endothelial function in junior doctors in a busy tertiary referral hospital. **Materials and Methods:** A prospective single arm study of junior doctors working in a busy tertiary referral hospital was conducted. Junior doctors aged between 25 years and 50 years were recruited to have their brachial artery flow mediated vasodilatation (BAFMD) assessed on the morning, before and after being on-call for 24-hours. Blood supply to the forearm was occluded for 5 minutes and the brachial artery diameter was measured at 1, 2, 3 and 5 minutes post cuff deflation, using a duplex Doppler ultrasound. A within-participant (paired) analysis was performed to compare diameter changes at all time intervals. **Results:** BAFMD in junior doctors after a 24-hour on-call was significantly attenuated when compared to pre-call BAFMD. This trend was significant at 2 minutes (p=0.03) and 3 minutes (p=0.003) hyperaemic response after cuff release. Analysis on variables such as duration of sleep (<5hrs), gender, racial origin of junior doctors were all significant factors for attenuation of BAFMD after a period of 24 hours on-call. **Conclusion:** The effect of stress of a 24-hour on-call has significant adverse effects on BAFMD in junior doctors working in a busy tertiary referral hospital. This adverse effect is significantly more prominent in junior doctors who had less than 5 hours of sleep of male gender, of Malay racial origin and of single marital status.

Keywords: Endothelial function, brachial artery flow mediated vasodilatation, junior doctors, stress, on-call

INTRODUCTION

Psychosocial stress, such as social isolation, chronic life stress, personality traits, characters traits and mental stress (such as depression and anxiety), play significant roles in the aetiology and pathogenesis of a wide range of cardiovascular diseases. [1–5] Its direct influence on the physiology of the nervous (through excessive sympathetic stimulation),

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endocrine and immune systems in the long-term has been linked to the pathogenesis of endothelial dysfunction and atherosclerosis. [4, 6] Beside these direct influences, the negative effects of stress lead to the adoption of a sedentary and unhealthy life style such as poor diet and smoking. [4, 7]

Stress as a modifiable risk factor for cardiovascular disease has been well studied. Exposure to stressful events has been shown to cause endothelial dysfunction, the early progenitor for atherosclerosis and cardiovascular diseases. [8–10] In a study of 402 university students between the age of 18 and 25 years in Portugal, the prevalence of hypertension was 24.9% in the study group and of those who were exposed to stress, 27.2% had isolated systolic hypertension. [11] Epidemiological data from several large international studies have reported that individuals reporting exposure to high levels of psychosocial stress have significantly elevated risk of developing cardiovascular diseases, with odds ratio for myocardial infarction as high as 2.5. [3]

Work-related stress from high work demand with persistent high sympathetic stimulation have also been associated with endothelial dysfunction, coronary heart disease morbidity and mortality, with increased atherosclerotic index as indicated by progression of carotid artery intima-media thickness and recurrent ischaemic events. [12, 13] The findings of the prospective Women's Health Study recently reported that women with high job-related stress have twice the risk of myocardial infarction compared to those with lower job-related stress, and were 43% more likely to undergo heart surgery.

Health professionals such as doctors are constantly exposed to high levels of work-related stress in their daily activity, particularly during a 24-hr on-call session. The physical as well as mental stress encountered with high work demand and professional responsibility in physicians have been shown to be associated with increased inflammatory markers which could be a pathway leading to cardiovascular pathology. [6] However the effects of such high level work-related stress on endothelial function of doctors have not been well studied previously. Thus this study primary aim is to investigate the adverse effects of work-related stress associated with a 24-hr on-call, in particularly sleep deprivation on endothelial function, in junior doctors working in a busy tertiary referral hospital.

MATERIALS AND METHODS

Study Population: Thirty junior doctors (Pre-Registration House Officers [PRHOs], Medical Officers [MOs] and Senior Medical Officers [SMOs]), aged between 25 years and 50 years, working at a busy tertiary referral hospital, the 'Raja Isteri Pengiran Anak Saleha Hospital (RIPASH)', were recruited to undergo a prospective single arm study to investigate the effect of on-call stress on vascular endothelial function which can be used as an indicator of vascular health before and after a period of 24-hours on-call. The doctors were each given a 'Participant Information Sheet' and upon agreement, were asked to sign a "Written Informed Consent Form" as part of their recruitment. Each recruited doctor underwent two separate assessments, once on the morning before their on-call duties or on the morning of the third day following their last on-call duties (pre-call assessment); and another on the morning immediately after completing their 24-hr on-call duties (post-call assessment). Participants' demographic data such as gender, age, grade of junior doctor, total duration of hours of sleep, number of sleep interruptions, number of on-calls per month and total number of duty hours per week were collected.

Study Design and Protocol: Participants were required to fast and withhold from any agents that could affect vascular reactivity, which included analgesics, lipid-lowering medications, antihypertensives, anticoagulants, nitrates, caffeine (coffee, tea, etc.), aspirin, and non-steroidal anti-inflammatory drugs from midnight prior to the morning of the study. [14, 15] Doctors with a past history of cardiovascular disease such as hypertension or diabetes and who were on antihypertensive or diabetic medications were excluded. All studies (pre and post-call) were conducted between 07.30 am and 08.30 am prior to starting their clinical duties in a quiet room at 22-24°C after resting for 20 minutes in a supine position with their left arm fully extended and cradled in a silicon filled mould to prevent movement during the study. A tourniquet pressure cuff (Tourniquet 2500 ELC, VBM Medizintechnik, Germany) was placed 5-10cm above the antecubital fossa of the left arm. A blood pressure cuff was placed on the right upper arm to monitor blood pressure before and after the procedure. An oxygen saturation probe was attached to the right thumb of the participant to monitor oxygen saturation and heart rate throughout the study.

A linear 7.5 MHz vascular transducer (S-Nerve™ Ultrasound, Sonosite Inc., USA) was used to acquire a longitudinal image of the brachial artery. Once visualised, the position of the transducer was marked. The distance between the tip of the thumb and cubital crease was measured and used as a reference point for the subsequent study to ensure the same segment of brachial artery was imaged and measured.

The best possible segment of the brachial artery was obtained and the image frozen at maximal systole; indicated by maximum dilation of the artery. The diameter of the artery was measured at 3 points from intima to intima using edge-to-edge tracking software. After this, the tourniquet cuff was inflated to 100mmHg above the systolic blood pressure for 5 min. After 5 minutes, the cuff was deflated and the ischaemic hyperaemic response of the brachial artery was measured at intervals of 1, 2, 3 and 5 minutes.

Statistical Methods: All data were entered and analysed using SPSS version 16.0. The calculated study sample size was 30 based on a power of 80%, an alpha of 0.05, to detect an expected difference in BAFMD of 4.0% and an estimated standard deviation of 7.5%. [8] BAFMD was calculated as the percentage change from baseline readings by subtracting the post-cuff readings at the various time intervals from baseline and divided by baseline readings. [14, 15] The pre-call and post-call percentage changes (as compared to the baseline in BAFMD of participants were compared using the paired t test for all time intervals. Variables such as gender, duration of sleep, grade of junior doctors, marital status and surgical versus medical specialties were also assessed for statistical significance using univariate analysis. Two-sided hypothesis testing was used and p less than 0.05 was considered to be statistically significant.

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RESULTS

Table 1 shows the socio-demographics of the study group of 30 doctors, with a mean age of 33.2 ± 8.7 years.

Table 1: Demographics of subjects.

Variables	*n* (%)	Mean (SD)
Age (year)		33.2 ± 8.7
Gender		
Male	19 (63.0)	
Female	11 (37.0)	
Race		
Malay	15 (50.0)	
Chinese	5 (17.0)	
Indian	10 (33.0)	
Marital Status		
Single	11 (36.7)	
Married	18 (60.0)	
Divorced	1 (3.3)	
Department		
Internal Medicine	11 (36.7)	
Surgical	19 (63.3)	
Medical Ranking		
FY Pre-Registration HO	6 (20.0)	
Medical Officer	18 (60.0)	
Senior Medical Officers	6 (20.0)	

FY: Foundation year, HO: House Officer

Effects of On-call Stress on percentage change of BAFMD:

Table 2 shows the mean percentage change of BAFMD for both pre and post on-call studies at the various time intervals, with maximal vasodilation achieved at 2 minutes following cuff deflation (pre on-call: 16.1%; post on-call: 12.7%). There were significant reduction of percentage change of BAFMD in the post on-call measurements achieved at 2 minutes (p=0.030) and at 3 minutes (p=0.003) when compared with the pre on-call measurements (Figure 1), indicating failure of the endothelium to achieve maximum vasodilation in response to ischaemic stimuli after a 24-hour on-call duty.

Factors Affecting BAFMD

Total duration of sleep

The mean duration of sleeps during on-call duties was 4.4 ± 1.6 hours (Table 3) for the whole group. Doctors who had less than 5 hours of sleep (Group 1) showed significant depression of BAFMD between pre and post-call measurements at 2 minutes (p=0.028) and 3 minutes (p=0.049). On the other hand, doctors who had more than 5 hours of sleep (Group 2) did not show any significant differences in percentage change of BAFMD at all time intervals (Table 4). There were no differ-

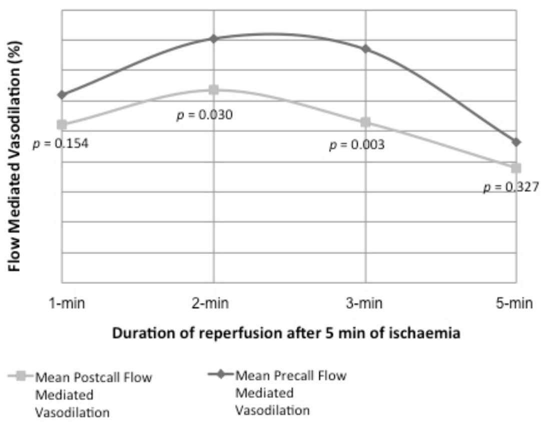

Fig. 1: Percentage changes of BAFMD and their level of significance.

Table 2: Effects of 24-hr On-call Stress on percentage change of BAFMD (*n* = 30).

Time after cuff deflation	Pre-call BAFMD	Post-call BAFMD	Mean of BAFMD difference α (95% CI)	*t* Statistics β (*df*)	*p* value β
1 Minute	12.4 ± 7.45	10.40 ± 5.20	(-0.8, 4.6)	1.46 (29)	0.15
2 Minute	16.1 ± 7.20	12.70 ± 5.02	(0.3, 6.5)	2.28 (29)	0.03*
3 Minute	15.4 ± 8.13	10.58 ± 5.16	(1.8, 7.9)	3.24 (29)	0.003**
5 Minute	9.3 ± 9.56	7.58 ± 5.87	(-1.8, 5.3)	1.00 (29)	0.33

BAFMD: brachial artery flow mediated vasodilatation

Table 3: Variables of the two groups based on total duration of sleep hours.

Variables	*Whole Group N=30*	*Group 1 <5hr N=18*	*Group 2 >5hr N=12*	*p*
Mean total duration of Sleep (hr)	4.4 ± 1.6	3.43 ± 1.01	5.92 ± 1.06	*<0.001*
Mean total number of sleep interruption	2.27 ± 1.98	2.67 ± 2.14	1.67 ± 1.61	*>0.05*
Mean number of on-call sessions per month	4.9 ± 1.3	4.59 ± 1.46	5.23 ± 1.01	*>0.05*

Table 4: Percentage change in BAFMD in Doctors according to total duration of sleep hour.

	Group 1 <5hrs (n=18)			**Group 2 ≥5hrs (n=12)**		
Mean BAFMD % change	**Pre-call Median (IQR)**	**Post-call Median (IQR)**	**p**	**Pre-call Median (IQR)**	**Post-call Median (IQR)**	**p**
@ 1 min after cuff deflation	11.6 (10.8)	12.6 (10.0)	0.22	9.1 (10.2)	8.3 (7.7)	0.75
@ 2 min after cuff deflation	15.5 (9.4)	11.1 (5.6)	0.028*	13.5 (6.2)	13.3 (6.8)	0.75
@ 3 min after cuff deflation	15.9 (11.9)	11.6 (6.8)	0.049*	14.6 (9.1)	9.2 (9.5)	0.1
@ 5 min after cuff deflation	7.1 (9.1)	6.3 (6.1)	0.45	8.5 (12.6)	67.4 (12.3)	0.81

ences in the number of times of sleep interruptions or the number of on-calls per month between the two groups (Table 3).

Gender

Male doctors showed a significant reduction of percentage change of BAFMD between pre and post on-call readings at 3 minutes (*p*=0.014). There were no significant changes in female doctors. The results between genders are summarised in Table 5.

Race

Malay doctors showed a significant reduction of percentage change of BAFMD between pre and post on-call at 3 minutes (*p*=0.017). There were no significant changes observed among Indian doctors. The results are summarised in Table 6. Chinese doctors were not compared due to the small number.

Table 5: Percentage change in BAFMD in Doctors according to gender.

	Male (n=19)			**Female (n=11)**		
Mean BAFMD % change	**Pre-call Median (IQR)**	**Post-call Median (IQR)**	**p**	**Pre-call Median (IQR)**	**Post-call Median (IQR)**	**p**
@ 1 min after cuff deflation	10.8 (10.9)	8.5 (8.5)	0.16	11.2 (12.1)	13.8 (9.4)	0.93
@ 2 min after cuff deflation	13.5 (4.5)	11.2 (5.1)	0.053	16.3 (11.8)	14.7 (10.8)	0.86
@ 3 min after cuff deflation	14.7 (11.1)	11.4 (8.1)	0.014*	16.1 (15.9)	9.4 (8.6)	0.29
@ 5 min after cuff deflation	8.1 (9.6)	5.9 (10.6)	0.11	4.6 (15.3)	8.3 (8.5)	0.48

Table 6: Percentage change in BAFMD in Doctors according to race.

	Malay (n=11)			**Indians (n=10)**		
Mean BAFMD % change	**Pre-call Median (IQR)**	**Post-call Median (IQR)**	**p**	**Pre-call Median (IQR)**	**Post-call Median (IQR)**	**p**
@ 1 min after cuff deflation	16.6 (12.1)	11.0 (12.6)	0.07	10.8 (5.8)	8.3 (8.7)	0.58
@ 2 min after cuff deflation	17.1 (10.9)	11.9 (7.5)	0.16	13.1 (2.2)	12.2 (6.2)	0.72
@ 3 min after cuff deflation	18.9 (7.5)	11.2 (9.0)	0.014*	13.3 (10.1)	9.6 (5.3)	0.37
@ 5 min after cuff deflation	7.3 (10.7)	6.9 (9.1)	0.65	6.9 (11.0)	5.9 (6.1)	0.65

Table 7: Percentage change in BAFMD in Doctors according to their marital status.

	Single (n=11)			Married (n=18)		
Mean BAFMD % change	**Pre-call Median (IQR)**	**Post-call Median (IQR)**	**p**	**Pre-call Median (IQR)**	**Post-call Median (IQR)**	**p**
@ 1 min after cuff deflation	11.2 (14.3)	15.6 (8.9)	0.66	10.8 (8.9)	7.7 (8.1)	0.08
@ 2 min after cuff deflation	16.3 (8.9)	14.7 (11.6)	0.98	13.4 (6.5)	11.1 (5.0)	0.12
@ 3 min after cuff deflation	16.1 (7.6)	8.5 (9.2)	0.050*	14.8 (15.8)	10.5 (6.5)	0.07
@ 5 min after cuff deflation	8.1 (10.2)	6.4 (6.5)	0.18	6.7 (9.8)	6.2 (8.8)	0.71

Marital Status

Doctors who are single showed significant reduction between pre and post on-call readings only at 3 minutes (p=0.050) but no significant difference was observed in married doctors. These are shown in Table 7.

Department of Work

Working in the different departments did not have any effects in percentage change of BAFMD between pre and post on-call readings (Table 8).

Haemodynamic Parameters

All haemodynamic parameters during the studies were stable and there were no significant changes between pre and post on-call haemodynamic parameters (Table 9; $p > 0.05$).

DISCUSSION

BAFMD is a surrogate indicator of the health of the vascular endothelium. Early endothelium dysfunction characterised by reduced endothelium-mediated vasodilation has been shown to be associated with early atherosclerosis and long-term cardiovascular events. [16] Junior doctors have been known to work long hours in stressful work environments and the participants in this study worked a mean (SD) of 57.6 (5.4) hours per week with mean (SD) number of on-calls at 4.9 (1.3) per month. This is well above the recommended European working times directives of 48 hours. Hence such physical and mental work-related stress, particularly during a 24-hour on-call session can have detrimental effects on the health of junior doctors. This study has shown that the stress associated with a 24-hour on-call has significant adverse effects on the BAFMD in hospital junior doctors, on the morning after the on-call duties.

The morning post on-call BAFMD measurements in junior doctors generally showed a decreasing trend at all time intervals compared with pre on-call BAFMD readings, but were significantly depressed at the 2nd and 3rd minute of reperfusion hypereamia (Figure 1). This finding suggests that the

Table 8: Percentage change in BAFMD in Doctors based on Departments.

	Surgery (n=19)			Medical (n=11)		
Mean BAFMD % change	**Pre-call Median (IQR)**	**Post-call Median (IQR)**	**p**	**Pre-call Median (IQR)**	**Post-call Median (IQR)**	**p**
@ 1 min after cuff deflation	10.8 (10.7)	8.5 (7.1)	0.26	12.3 (12.1)	13.6 (13.0)	0.53
@ 2 min after cuff deflation	13.5 (9.4)	13.5 (6.1)	0.47	15.7 (11.2)	10.3 (3.9)	0.06
@ 3 min after cuff deflation	14.7 (7.9)	11.9 (6.1)	0.058	17.1 (14.9)	8.2 (3.6)	0.09
@ 5 min after cuff deflation	7.7 (10.5)	8.6 (8.0)	0.78	4.6 (6.6)	5.0 (4.7)	0.25

stress associated with a 24-hour period of on-call was associated with significant degree of endothelial dysfunction, as much as 5% reduction in BAFMD.

The results of this study are consistent with other related studies that focused on investigating the adverse effects of stressful events on BAFMD. In a study conducted by Miller *et al*., they reported similar findings where BAFMD was reduced in volunteers after the cinematic viewing of movie clips that caused mental stress. [9] The authors believe this occurred due to impairment to nitric oxide vasodilation. Ghiadoni *et al*. had also concluded that brief episodes of mental stress causes transient endothelial dysfunction and hypothesized the existence of a link between mental stress and atherogenesis. [8] In another study of 15 medical residents in cardiology, Garcia-Fernandez *et al.* concluded that the stress caused by 24-hours on-call in a cardiology emergency room depresses or abolishes endothelial function. [12]

However, this study showed that significant reduction in BAFMD was seen only in junior doctors who had less than 5 total sleep hours, implicating stress associated with sleep deprivation as the most significant factor in causing endothelial dysfunction in junior doctors after a 24-hour period of on-call duties. This finding is irrespective of the number of sleep interruptions, number of on-calls per month and mean total number of duty hours per week. As a matter of fact, the group who had 5 or more hours of sleep had more on-calls or mean total number of duty hours per week. The implication of this finding is important as it shows that the stress related to the physical and mental component of being on-call can be negated by having sufficient hours of sleep, specifically 5 or more hours.

Takase *et al.* also reported similar endothelial dysfunction in 30 healthy male college students who were sitting for their examinations. They concluded that the stress of sleep deprivation during the four week-long final examination period had significant adverse effect on the students' BAFMD. [10] Thus sleep is an important component in our biological adaptation to stress by allowing the body to recover if given sufficient time to do so.

Other factors found to have a significant impact on BAFMD were male gender, Malay doctors and single marital status. All of factors were associated with significant reduction in BAFMD after a 24-hour on-call session at the 3rd minute of reperfusion. This study indicates that of being female gender and married may in someway help a doctor to cope better with the stress of being on-call in a busy tertiary referring hospital.

Table 9: Recorded haemodynamic parameters pre and post on-call.

	Pre on-call Pre-procedure Mean (SD)	Post on-call Pre-procedure Mean (SD)	Mean of Difference α (95% CI)	*t* Statistics β (*df*)	*p* value β
Blood Pressure					
Systolic	111.2 (10.28)	112.2 (9.98)	(-4.4, 2.4)	-0.60 (29)	0.56
Diastolic	70.2 (9.46)	71.9 (9.35)	(-5.3, 1.9)	-0.98 (29)	0.34
Heart Rate	68.5 (11.08)	71.4 (10.97)	(-9.0, 3.3)	-0.96 (29)	0.35
Oxygen Saturation	99.1 (0.85)	99.3 (0.55)	(-0.6, 0.1)	-1.37 (29)	0.18

Changes in the heart rate and blood pressure during the study can affect BAFMD. Thus all 30 participants had their blood pressure and heart rate monitored throughout the study. Analysis of data did not show any significant difference between the pre on-call blood pressure and heart rate readings with the post on-call readings. Thus changes in blood pressure or heart rate is unlikely to account for the differences observed in BAFMD between pre on-call and post on-call findings.

The main study limitation is the unequal representation of doctors from each specialty whereby the majority of junior doctors in this study were from the surgical specialties with only a limited number from the medical specialty. It is for this reason also that there is a majority of male doctors compared to female doctors.

In conclusion, our study showed that the effect of stress of a 24-hour on-call duty has adverse effects on the endothelial function in junior doctors working in a busy tertiary referral hospital. This adverse effect is significantly more prominent in male doctors, those who are not married, are of Malay origin and who had less than five hours of sleep. However this negative effect can be negated by having five or more total hours of sleep. This finding has significant implications in policy making in terms of arranging on-calls for junior doctors to ensure that all hospital doctors should get at least five or more hours of sleep for every on-call session.

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