

# Exaggerated blood pressure reactivity in the offspring of first-cousin hypertensive parents

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## زيادة رد الفعل لضغط الدم في أبناء زيجات أولاد العمومة من الدرجة الأولى من ذوي ضغط الدم المرتفع

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**الملخص: الهدف:** دراسة معدل ضغط الدم الأساسي ورد الفعل لهذا المعدل في صغار السن من أبناء زيجات أولاد العمومة من الدرجة الأولى ذوي ضغط الدم الطبيعي أو المرتفع ومقارنتهم مع أبناء زيجات ليست بينهم صلة قرى وذوي ضغط دم مرتفع. **الطريقة:** تم قياس ضغط الدم ونبض القلب ومعدل البدانة في الذكور من الأطفال في عامهم التاسع أو العاشر من العمر. كان ١٩ منهم أبناء لوالدين أبناء عم من الدرجة الأولى ذوي ضغط دم طبيعي ، و١٦ منهم أبناء لوالدين أبناء عم من الدرجة الأولى أيضا ولكنهم ذوي ضغط دم مرتفع ، ١٢ منهم أبناء لوالدين ليست بينهم قرابة دم وذوي ضغط دم مرتفع أيضا. **النتيجة:** أظهرت ذرية أبناء العمومة ذوي ضغط الدم المرتفع بأنهم أعلى ارتفاعاً في ضغط الدم الانقباضي والانسياطي لدى أول محاولة لقياس ضغط الدم في حياتهم ، كما أظهرت أن ذرية أبناء العمومة ذوي ضغط الدم الطبيعي لهم رد فعل أدنى بالمقارنة ، أما أطفال الوالدين الذين ليست بينهم صلة قرابة دم وذوي ضغط دم مرتفع فقد كان رد الفعل لديهم وسطياً بين المجموعتين السابقتين. **الخلاصة:** قد يكون للارتفاع الزائد في رد الفعل لضغط الدم عند أطفال الوالدين ذوي ضغط الدم المرتفع دلالات لما قد يكون عليه ضغط دم هؤلاء الأطفال مستقبلاً ، كما أن ذلك قد يكون مؤشراً مهماً وفعالاً لقابلية هؤلاء الأطفال للإصابة بضغط الدم المرتفع في مستقبل حياتهم.

**ABSTRACT. Objective:** To study blood pressure and blood pressure reactivity in young offspring of normotensive or hypertensive parents who are consanguineous (first cousins) or are not blood-related. **Method:** Blood pressure, heart rate and body mass index (BMI) were measured in 9–10 year-old male offspring of 19 pairs of first-cousins normotensive, 16 pairs of first-cousin hypertensive and 12 pairs of non-blood-related hypertensive parents. **Results:** The offspring of first-cousin hypertensive parents exhibited the greatest systolic and diastolic blood pressure reactivity to their first casual blood pressure measurement, while the offspring of first-cousin normotensive parents showed the least reactivity. The offspring of the hypertensive parents who were not blood-related showed an intermediate reactivity. Basal systolic blood pressure (SBP) was also highest in the offspring of first-cousin hypertensive parents, and their basal diastolic blood pressure (DBP) was higher than that in offspring of first-cousin normotensive parents. **Conclusion:** The augmented blood pressure response in the offspring of hypertensive parents may have prognostic implications and serve as an important and significant indicator of predisposition to hypertension later in life.

**Key words:** consanguineous marriage, offspring, blood pressure reactivity, Oman.

GENETIC INFLUENCE ON THE VARIABILITY OF blood pressure (BP) in populations has been well established.<sup>1-3</sup> This effect has been repeatedly demonstrated by strong evidence of familial aggregation of BP.<sup>3-9</sup> Significant correlations exist between offspring's and parent's blood pressure, and more so between twins.<sup>10-12</sup> This familial influence on BP can be detected from early childhood and tends to track over the years increasing in

magnitude as the child progresses towards adolescence.<sup>4,5,13</sup> Children of hypertensive parents have higher average systolic and diastolic BP than children of normotensive parents, and are about 3.8 times more likely to have high BP before the age of 55.<sup>1,14</sup> Research indicates that essential hypertension has origins in childhood.<sup>15</sup> Tracking studies have shown that children and adolescents with elevated BP, though not necessarily in the hypertensive range, may be at

increased risk for developing hypertension later in life.<sup>16–19</sup> It is therefore useful to identify such familial predisposition in the offspring of parents with high blood pressure.

Cardiovascular reactivity is defined as the change in BP, heart rate, or other haemodynamic parameters in response to physical or mental stimuli.<sup>20</sup> Exaggerated BP reactivity has been observed in patients with hypertension compared to normotensive subjects and has also been described in young people, usually in connection with risk factors of hypertension.<sup>20–24</sup> Such studies demonstrate that BP reactivity to laboratory stressors tends to aggregate in families.<sup>25–27</sup> Hypertensive and pre-hypertensive subjects with positive family histories of hypertension show greater BP reactivity to mental and physical stressors than do subjects with no family history and a matching basal BP.<sup>1</sup> Such excessive responses of BP to stress may be a risk factor for the development of hypertension and other cardiovascular morbidities.<sup>24,28,29</sup>

Among the various methods to measure BP reactivity is a simple one that takes advantage of the 'white coat effect', the exaggerated BP response that many people exhibit when examined in a clinical setting. The difference between an individual's 'clinic BP' and the his 'daytime average 24-hour BP' can be used to quantify his BP reactivity due to the white coat effect.<sup>30,31</sup> In our study, we investigated whether familial similarity could be detected via casual BP estimations in the offspring of consanguineous marriage of hypertensive parents—a unique sample from the population that runs the highest risk of developing hypertension, and therefore in our opinion may provide a better approximation of the extent to which familial aggregation of BP can be expressed than all models studied before. This excellent opportunity was rendered possible by a strong cultural disposition in the Arab Gulf region towards consanguineous marriages. In Oman, a 1995 survey estimated that first-cousin marriages under the age of 50 years formed 34% of the total marriages.<sup>32</sup>

## METHOD

The participants were 135 schoolboys aged 9–10 years who were taking part in a summer sports camp in the city of Muscat. After obtaining parental consent to the study, a screening examination was conducted within the offices of the sports complex by a qualified cardiovascular technician who did not wear a white coat. The SBP, DBP, and heart rate were recorded from the left arm, for the first time ever in those children, using an automated device (PROPAQ, 102; Protocol Systems Inc, OR, USA). One measurement was taken after 10 minutes of supine rest, and another after 30

minutes. For each measurement the mean of two readings were calculated, however, if the first two readings differed by 3 mm Hg or more, a third reading was taken and the mean of the three was used. BP reactivity was taken as the difference between the first (10 min) and the second (30 min) readings. Body mass index (BMI;  $\text{kg}\cdot\text{m}^{-2}$ ) was calculated.

After all examinations were completed, each participant carried home a short simplified questionnaire on his parents' blood relationships, and whether one or both were on antihypertensive treatment. Pairs were then divided into first-cousin parents and parents who were not blood-related. Forty one pairs were first-cousin parents, 6 pairs of whom did not report for BP measurement, and were excluded from the study. Thirteen first-cousin parents were already on antihypertensive medication, and 3 were newly diagnosed with a SBP $\geq$ 145 and/or a DBP $\geq$ 95 mmHg on two separate visits each, as confirmed later by an independent physician at Sultan Qaboos University Hospital. The occurrence of hypertension varied among the 16 first-cousin hypertensive parents: in 4 pairs both parents, in 2 pairs the mothers only, and in 10 pairs the fathers only were hypertensive. The normotensive group among the first-cousin parents comprised 19 pairs, and both parents had a SBP $\leq$ 130 and DBP $\leq$ 80 mm Hg. The incidence of hypertension also varied in the parent pairs who were not consanguineous: In 2 pairs both parents were hypertensive; in 8 pairs only the father and in 2, only the mother were hypertensive. In the non-consanguineous cohort all hypertensives were already on antihypertensive medication.

## DATA PRESENTATION AND ANALYSIS

The children were divided into three groups. The low risk (LR) group consisted of the offspring of first-cousin normotensive parents, the medium risk (MR) group comprised the offspring of one or two non-consanguineous hypertensive parents, and in the high risk (HR) group were the offspring of one or two first-cousin-related hypertensive parents. Mean first and second SBP and DBP and heart rate values of HR children were compared to the corresponding values of the MR and LR children.

Statistical analysis was performed using SPSS version 7.5 for Windows. To determine significance of the difference between the three groups, the independent sample T-test with 95% confidence interval was used. A p value  $<0.05$  was considered significant.

## RESULTS

One hundred and sixteen parent pairs (86%) responded to the questionnaire. The mean age of the fathers was 42

**Table 1.** Blood pressure, body mass index and heart rate of the three study groups

Parents	Normotensive first-cousins	Hypertensive, Not blood-related	Hypertensive first cousins
Risk level	Low	Medium	High
<b>N</b>	19	12	16
<b>Body mass index (Kg/m<sup>2</sup>)</b>	16 (0.4)	15.8 (0.7)	17.3 (1.1)
<b>Systolic blood pressure (mm Hg)</b>			
a) 10 minutes	108 (1)	[112 (1.3)*]*	117 (1.8)**]*
b) 30 minutes	98 (0.8)	[99 (1.0)]	[102 (2.5)*]*
<b>Diastolic blood pressure (mm Hg)</b>			
a) 10 minutes	64 (1.6)	71 (0.9)*	75 (1.6)*
b) 30 minutes	60 (0.6)	68 (0.9)*	65 (1.4)*
<b>Heart rate (beats/minute)</b>			
a) 10 minutes	81 (1.5)	86 (1.7)	86 (2.5)
b) 30 minutes	73 (1.6)	79 (1.3)	77 (1.5)

The values are means  $\pm$  SE in parentheses; LR – Low risk; HR – High risk; MR – Medium risk; N – Number of pairs. \* $p < 0.05$ ; \*\* $p < 0.01$ ; ( ) \* – comparing HR to LR; [ ] \* comparing HR to MR

years (range 29–47) which was significantly higher than that of the mothers (33, range 25–37),  $p < 0.05$ . The main findings in the offspring are shown in table 1. There was no significant difference between the BMI of the three groups of children. The HR children exhibited the highest first SBP compared to the MR and LR children ( $p < 0.05$  and  $p < 0.01$  respectively). The second SBP reading was also significantly higher in the HR children than in the MR and the LR groups ( $p < 0.05$  for both). Similarly the first DBP

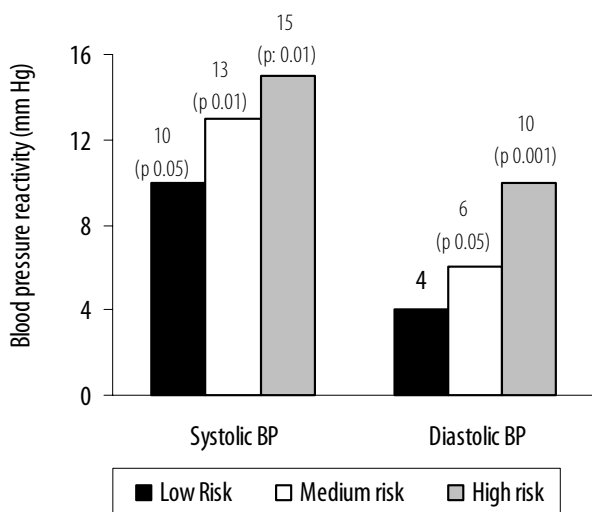
readings were significantly higher in the HR and MR than the LR groups ( $p < 0.01$  and  $p < 0.05$  respectively) with no significant difference between the HR and MR groups. The second DBP reading was also significantly higher in the HR and MR groups compared to the LR group ( $p < 0.05$  for both) with no significant difference between the readings in the HR and MR groups. There were no significant differences between the groups in the first and second heart rate estimations.

Figure 1 summarizes the SBP and DBP reactivity in the three groups. The HR group exhibited the highest SBP and DBP reactivity ( $p < 0.01$  and  $p < 0.001$  respectively) the MR group an intermediate reactivity ( $p < 0.01$  and  $p < 0.05$  respectively) while the LR group showed the least response with a slight but significant SBP reactivity ( $p < 0.05$ ) and non-significant DBP reactivity.

## DISCUSSION

All the subjects were of the same sex, similar BMI and age group, thereby eliminating the possible interaction of such factors. Our results show that a family history of hypertension did predict both the differential BP and BP reactivity in these children in accordance with the three group designations. HR children showed the greatest systolic and diastolic BP reactivity, MR children occupied an intermediate position, and the LR showed the least reactivity. These results are in agreement with other studies in which even milder levels of hypertensive heredity have revealed inclinations towards higher systolic and/or diastolic BP as well as higher BP reactivity to mental stress.<sup>26,34–38</sup> We can only speculate on the mechanism responsible for this variation between groups. Some studies have proposed that the exaggerated cardiovascular responses to stress are provoked by a differential sensitivity of adrenergic receptors and sympathetic overactivity.<sup>39,40</sup> Enhanced sympathetic activity may occur because of increased sympathetic stimulation and/or attenuated sympathoinhibition.<sup>41</sup> Overactivity starts in childhood and is easily evident in 30% of patients with incipient hypertension.<sup>40</sup> It is possible that there is a genetic component in sympathetic overactivity expressed with more vigour in high risk individuals. Although environmental factors do have a role in the development of high BP in humans, 50–79% of BP variations are attributed to genetic factors, and even this would probably be an underestimation in our and other similar populations.<sup>2,3,12</sup> The prevalence of consanguineous marriages in Oman places many of its children in the high risk group. Attention should therefore be drawn towards a probable high level of hypertension in this population.

One potential weakness of this study is that it is a

**Figure 1.** Blood pressure reactivity in children in the three risk categories

deductive one that compares the BP of the offspring of hypertensive and normotensive parents and not to the parents' actual BP values. Although most studies on the heritability of BP were based on estimations of casual BP readings, it is now accepted that 24-hour ambulatory BP monitoring is a superior clinical tool in predicting the basal BP since it may be less affected by artefacts such as the white coat effect.<sup>30,34,42</sup> Even though our technician did not wear a white coat, the children in our study were going through the experience for the first time in their lives, that too in a formal (office) setting, which could have elicited stress comparable to the white coat effect.<sup>43</sup> With this assumption we recorded the first round of BP measurement, after giving each child 10 minutes of rest. The 30-minute gap before the second BP measurement was to allow the child's BP to settle to its basal level. We acknowledge that this setting was sub-optimal for estimating basal BP, and cannot confirm that the casual reading after 30 minutes is a 'true' representative of basal levels: it still might have been confounded with the white coat effect. However, the setting was consistent for both the measurements and in all groups of children. Moreover it has been shown that the artefact inherent in both casual BP and basal readings is heritable and appears to aggregate in first-degree relatives.<sup>42</sup>

### CONCLUSION

The augmented BP reactivity found in the offspring of hypertensive parents might have prognostic implications and serve as an important early sign of familial predisposition to hypertension. Our findings emphasise the need for special follow up of children with family histories of hypertension, and for a national educational programme on the genetic risks of consanguineous marriages.

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