

# The low plasma testosterone levels of young Indian infarct survivors are not due to a primary testicular defect

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**Summary:** A case control study was performed to determine whether the hypotestosteronaemia described in men with coronary artery disease could be the result of primary testicular dysfunction. Testicular function was assessed by comparing the response of 10 young Indian men with myocardial infarction to human chorionic gonadotrophin (HCG) injection to that of 10 healthy age and weight matched controls.

The basal testosterone levels in the patients were significantly lower ( $12.71 \pm 1.36$  nmol/l vs  $16.51 \pm 0.79$  nmol/l;  $P=0.01$ ) and the basal oestradiol levels significantly higher than the controls ( $120.67 \pm 8.81$  pmol/l vs  $94.05 \pm 8.23$  pmol/l;  $P=0.02$ ). There was no difference in the sex hormone binding globulin concentrations. However, following HCG stimulation the patients demonstrated a normal response with a 2-fold increase in testosterone. There was no difference in the testosterone and oestradiol levels of the patients and controls following HCG stimulation.

This normal response in our patients demonstrates that the hypotestosteronaemia in Indian men with myocardial infarction is not due to a primary testicular dysfunction but probably is a result of increased aromatization of testosterone to oestradiol.

## Introduction

We have previously shown that young Indian men with coronary artery disease have significantly lower levels of plasma testosterone and an elevated oestradiol to testosterone ratio as compared to matched controls.<sup>1</sup> Although hypotestosteronaemia in patients with coronary artery disease has been demonstrated by other investigators,<sup>2,3</sup> the majority of reports on sex hormone levels have noted hyperoestrogenaemia with normal testosterone levels.<sup>4–6</sup>

The cause for the low levels of testosterone in men with coronary artery disease is not known, whereas the hyperoestrogenaemia has been assumed to be due to increased peripheral conversion of testosterone to oestrogen.<sup>4,7</sup> Whilst this assumption may also explain the low testosterone levels, none of the previous studies examined the possibility of primary testicular dysfunction being responsible for the hypotestosteronaemia.

artery disease and 10 matched healthy controls, in order to determine whether primary testicular dysfunction may be responsible for the hormonal aberrations seen in men with coronary artery disease.

## Patients and methods

Ten Indian male patients between the ages of 25–40 years with documented myocardial infarction and with angiographic evidence of significant coronary artery disease as previously described<sup>1</sup> were studied a year after the acute episode of myocardial infarction. None of the patients was in cardiac failure and all had returned to their occupation at the time of the investigation. The controls were healthy Indian male members of the hospital staff. The diet and exercise patterns of the controls were similar to the patients. None of the controls was on drugs. Some of the patients were on one or more of the following drugs: glyceryl trinitrate, beta-blockers, calcium channel blockers and glibenclamide. We have previously shown that these drugs have no effect on sex hormone levels.<sup>1</sup> After

The present report describes investigations carried out in 10 young Indian men with coronary

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Accepted: 16 December 1987

obtaining basal samples for oestradiol and testosterone, 3000 IU of human chorionic gonadotrophin (HCG) was administered intramuscularly and further samples obtained at 72 hours.<sup>8</sup> Blood sampling was performed between 0800 to 0900 h to avoid any diurnal variations. The methods used to assay oestradiol and testosterone have been previously described.<sup>9</sup>

Height and weight were measured and relative body weight was calculated using the formula weight(kg)/height(m).<sup>2</sup>

All data are expressed as mean  $\pm$  standard error of means (s.e.m.). Statistical analyses for the significance of the difference between means were performed by Student's *t* test. In addition 95% confidence intervals were given for differences in means where relevant. Significance was defined at the 5% level.

The study was approved by the hospital administration board and informed consent was obtained from all subjects.

## Results

The patients and the controls were matched with respect to age, body mass index and smoking history (Table I). The patients had significantly higher basal oestradiol and significantly lower basal testosterone levels as compared to the controls

**Table I** Salient clinical findings in patients and controls

	Patients	Controls	<i>P</i> value
Age (years)	35.6 $\pm$ 0.7	36.2 $\pm$ 1.1	0.33
BMI*	25.4 $\pm$ 0.7	25.4 $\pm$ 0.8	0.50
Smoking†	11.2 $\pm$ 1.8	13.1 $\pm$ 2.7	0.30

Data are mean  $\pm$  s.e.m.; \*Body mass index; †Number of cigarettes smoked per day.

**Table II** Basal sex hormone levels and their response to HCG stimulation

	Patients	Controls	95% CI*	<i>P</i> value
<b>Basal:</b>				
Oestradiol (pmol/l)	120.67 (8.81)	94.05 (8.23)	1.32 to 51.92	0.02
Testosterone (nmol/l)	12.71 (1.36)	16.51 (0.79)	-7.12 to -0.48	0.01
SHBG (nmol/l)	45.4 (1.74)	43.78 (2.87)	-7.67 to 10.91	NS
<b>Post HCG:†</b>				
Oestradiol (pmol/l)	249.99 (32.67)	271.08 (33.52)	-119.37 to 77.1	NS
Testosterone (nmol/l)	31.91 (2.89)	35.42 (3.26)	-12.67 to 5.65	NS
SHBG (nmol/l)	48.05 (2.1)	46.44 (2.67)	-6.63 to 9.85	NS

Data are mean (s.e.m.); HCG - human chorionic gonadotrophin; \*Confidence intervals; †=72 hours following injection of human chorionic gonadotrophin; SHBG - sex hormone binding globulin. NS - not significant..

(Table II), whilst there was no significant difference in the sex hormone binding globulin (SHBG) levels. The basal oestradiol to testosterone ratio in the patients (10.32  $\pm$  1.19) was significantly higher than the controls (5.84  $\pm$  0.60; *P* < 0.005; 95% CI 1.67 to 7.29). Following HCG stimulation the oestradiol and testosterone levels of the patients were similar to those in the controls.

## Discussion

The aim of this study was to determine whether primary testicular dysfunction is a possible cause for the hypotestosteronaemia demonstrated in Indian men with coronary artery disease.<sup>1</sup> The results of this study confirmed the presence of hypotestosteronaemia and, in addition, demonstrated significant hyperoestrogenaemia in the patients. Obesity, drugs and cigarette smoking have all been implicated as possible causes for the hormonal disturbances seen in men with coronary artery disease.<sup>10,11</sup> These factors were not operative in this study as our patients were closely matched with the controls with respect to ethnic origin, age, relative body weight and cigarette smoking. Furthermore the degree of physical activity of the controls was similar to the patients and so was their dietary history. No other exogenous factor to account for the hormonal disturbance could be identified in our patients. The observed hormonal disturbances in our patients cannot be attributed to disturbances in SHBG binding capacity since SHBG levels in the patients were similar to those of the controls.

Testosterone is essentially secreted by the testes and a major source of oestradiol in men is by conversion of testosterone to oestradiol via aromatization in muscle and adipose tissue.<sup>12</sup> The testosterone response to HCG stimulation is a

reliable and good index of the integrity of the testis. While the conventional HCG test entails a 5 day procedure with repeated injections of HCG it has recently been shown that a more rapid test requiring only one sample 72 hours following HCG injection is just as reliable.<sup>8</sup> In the present study both the patients and the controls demonstrated normal responses, i.e. at least a two-fold increase in testosterone.<sup>8</sup> This response clearly suggests that testosterone secretion in our patients with coronary artery disease is normal. The testosterone as well as the oestradiol levels in the patients following HCG stimulation were similar to the controls. This demonstration of normal testicular response to HCG stimulation in men with coronary artery disease lends support to the postulate that increased aromatization of testosterone to oestradiol may be responsible for the basal hypotestosteronaemia noted in our patients. This reaction will in effect reduce the serum testosterone level and cause a secondary increase in oestradiol levels.

The reason for this increased conversion of testosterone to oestradiol in men with coronary artery disease is not known and will require further investigation. A possible mechanism is suggested by

an *in vitro* study which demonstrated increased aromatization of testosterone to oestradiol by the addition of noradrenaline to Sertoli cell-enriched cultures.<sup>13</sup> This report is of interest as significant elevation of serum noradrenaline levels has been reported in men with myocardial infarction.<sup>14</sup> It is feasible that the increased levels of noradrenaline in patients could stimulate aromatization and hence account for the hormonal disturbances described.

In conclusion, this study has demonstrated that the significantly lower plasma testosterone levels observed in young Indian men with coronary artery disease are not due to primary testicular dysfunction but probably due to increased peripheral conversion of testosterone to oestradiol.

#### Acknowledgements

We thank Dr P.K. Naidoo, Medical Superintendent of R.K. Khan Hospital for permission to publish, and the nursing staff of the coronary care unit for their cooperation. The investigations undertaken in this study were performed in the M.R.C. Preclinical Diagnostic Chemistry Research Unit.

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