Left ventricular outflow tract obstruction: should cardiac screening be offered to first-degree relatives?

Wilhelmina S Kerstjens-Frederikse,¹ Gideon J Du Marchie Sarvaas,² Jolien S Ruiter,¹ Peter C Van Den Akker,¹ Arno M Temmerman,² Joost P Van Melle,² Robert M W Hofstra,¹ Rolf M F Berger²

ABSTRACT

Objectives To determine whether offering cardiac screening to relatives of patients with left ventricular outflow tract obstructions (LVOTOs) would be justified.

Background LVOTOs have been recognised as a group of congenital heart diseases with 'high heritability'. One of the LVOTOs, the bicuspid aortic valve, is often asymptomatic, but has become known to be associated with sudden, unexpected cardiac death. However, the need for cardiac screening of first-degree relatives of patients with LVOTO has not been determined owing to the lack of studies in well-defined cohorts of consecutive patients.

Methods The families of a cohort of 249 consecutive paediatric patients with LVOTO were offered genetic counselling. Of 182 consenting index patients, 40 patients (22%) appeared to have associated non-cardiac congenital anomalies (LVOTO-NCA). In the other 142 patients with LVOTO, cardiac screening of 449 first-degree relatives was performed.

Results Cardiac screening disclosed a cardiac anomaly in 34 first-degree relatives (8%). In 23 (68%) of these the cardiac anomaly was a bicuspid aortic valve. Twenty-four of these anomalies were newly detected by our screening programme (71%). These 34 cardiac anomalies were found in the families of 28 index cases (8%). In 23 (68%) of these the cardiac anomaly was a bicuspid aortic valve.

Conclusions This study shows that of the patients with LVOTO without NCA, 20% had (an) affected first-degree relative(s), frequently with undetected bicuspid aortic valves. These data suggest that cardiac screening of relatives of patients with LVOTO without NCA is justified. This may help prevent sudden, unexpected, cardiac death or life-threatening complications in relatives with undetected bicuspid aortic valves.

INTRODUCTION

Left ventricular outflow tract obstructions (LVOTOs) form a group of congenital heart diseases that are generally considered a genetic entity with a high heritability.¹ ² The frequency of cardiac anomalies in first-degree relatives, however, has not been studied in well-defined, consecutive patient cohorts. Therefore, the yield of cardiac screening of relatives cannot be assessed using data of previous studies.

LVOTOs are congenital anomalies of the left chamber, the mitral and/or aortic valve, and/or the ascending aorta. A bicuspid aortic valve (BAV), which occurs in approximately 1% of the population,³ ⁴ is included in this group, although it may not be obstructive. Congenital aortic valve stenosis, often caused by BAV, coarctation of the aorta (COA) and hypoplastic left heart syndrome (HLHS) together occur in 8/10000 live born children.² Other, less prevalent LVOTOs include mitral valve stenosis, subvalvular or supravalvular aortic stenosis and interruption of the aortic arch. This group of LVOTOs is considered a genetic entity, because various LVOTO diagnoses may occur within families.⁵ ⁶

Like other congenital heart defects, LVOTOs may occur in combination with non-cardiac congenital anomalies (NCA).⁷ ⁸ ¹² Relatives of patients with NCA were not included in the cardiac screening programme, because the aetiology and heredity of syndromes with heart defects is likely to be different from non-syndromic heart defects.

In LVOTO without NCA, monogenic or more complex (oligogenic or multifactorial) models of inheritance have been suggested and though several loci and genes associated with LVOTOs have been published, the majority of the genes involved is unknown.⁵ ¹³ ⁻²²

The BAV, which is the LVOTO lesion with the highest prevalence but often remains unrecognised, is known to be associated with aortic aneurysm and sudden, unexpected cardiac death.²³ COA may present with complications such as premature myocardial infarction, cerebral vascular accidents or aortic dissection. To prevent such complications, early detection of these cardiac anomalies is needed. If an increased occurrence of these cardiac anomalies in first-degree relatives of consecutive patients with LVOTO indicates that these relatives are a high-risk population, cardiac screening of these people may be warranted.

This study aims to describe the occurrence of cardiac anomalies in first-degree relatives of patients with LVOTO, after thoroughly excluding patients with additional NCA. We present clinical data, including echocardiographic screening of first-degree relatives, of a well-defined cohort of consecutive paediatric patients with LVOTO and based on these data we propose a diagnostic strategy for patients with LVOTO and their families.

PATIENTS AND METHODS

A cohort of consecutive paediatric patients (n=249), aged between 0 and 18 years, with LVOTO was seen at the Centre for Congenital Heart Diseases, University Medical Centre Groningen (UMCG) between January 2006 and January 2009. The UMCG is a tertiary referral
centre for the northern and eastern part of the Netherlands, an area inhabited by approximately 5 000 000 people, with relatively low rates of immigration. A flow chart of the inclusion is shown in figure 1. The cohort included all paediatric patients with LVOTO younger than 18 years old seen both in the clinical wards and in the outpatient clinic during the study period. Terminations of pregnancy and intrauterine deaths were not included. All patients had a detailed cardiac evaluation by a paediatric cardiologist, including ECG and cardiac ultrasound/Doppler imaging. In patients with combined lesions the primary diagnosis was defined as the most relevant anomaly, so if a BAV and a COA were present, the diagnosis was coarctation. All stenotic, normally functioning, or insufficient bicuspid aortic valves were labelled BAV. HLHS was defined as underdevelopment of the left ventricle and ascending aorta together with anomalies of the mitral and/or aortic valve. The group ‘miscellaneous’ includes mitral valve stenosis without HLHS, subvalvular or supravalvular aortic stenosis and interruption of the aorta. All families were offered genetic counselling.

A detailed family history for at least three generations was recorded and, in the case of cardiac anomalies in relatives, these were verified by a written report from the relative’s cardiologist. All index patients were evaluated for NCA by a clinical geneticist (WSK-F). Patients with LVOTO-NCA were karyotyped by G-banding. If the karyotype was normal, and no specific diagnosis had been made, array-based comparative genomic hybridisation (whole genome array (WGA)) was performed using a 105 K Agilent oligonucleotide array (custom design ID:019015; Agilent Technologies Inc, Santa Clara, California, USA), according to the manufacturer’s protocols. The average resolution was approximately 20 kb. If a deletion was detected, it was confirmed by fluorescent in situ hybridisation (FISH) and the parents were also investigated. If NCA were detected, the relatives were excluded from the cardiac screening protocol, because LVOTO in the context of a de novo chromosomal anomaly or a syndrome was regarded unlikely to occur in asymptomatic relatives of patients with LVOTO-NCA.

All first-degree relatives of patients with LVOTO without NCA were offered cardiac evaluation by a (paediatric) cardiologist, including ECG and a detailed cardiac ultrasound study, including 2D, colour and spectral Doppler imaging, visualising the anatomic components of the left-sided cardiac structures: left atrium, mitral valve, left ventricular cavity, aortic valve, ascending aorta, aortic arch and isthmus. Transverse aortic root dimension was measured at the sinus Valsalva level from the leading edge of the anterior aortic wall (in accordance with the recommendations of the American Society of Echocardiography).24 If the aortic valve could not be visualised appropriately to judge the separate cusps, additional MRI was performed.

The study was approved by the UMCG ethics committee and all participating families gave their informed consent.

RESULTS

Of the 249 index patients eligible for the study, 182 patients and/or their parents consented to the family investigation (73%). The consenting index patients were 122 male and 60 female subjects (male/female ratio 2:1). NCA were detected in 40 of the 182 patients (22%), 25 male, 15 female. The 142 patients without NCA were 97 male subjects, 45 female subjects, aged 0.5–20.4 years on 1 January 2009 (mean age 8.5 years).

Cardiac diagnosis

The primary diagnosis in 182 index patients was BAV/aortic valve stenosis/aortic insufficiency in 65 patients (45 of these were bicuspid), HLHS in 19 patients, COA (with or without BAV) in 96 patients and miscellaneous in 2 patients. In figure 2 the diagnoses in patients are separated into patients with LVOTO without NCA (figure 2A) and patients with LVOTO-NCA (figure 2B). Diagnoses of patients who did not give consent are also shown (figure 2C). Apart from a relatively low number of HLHS diagnoses in this last group (only one), the distributions are similar.

Diagnoses in patients with LVOTO associated with NCA

We found 14 syndrome diagnoses in 40 patients with LVOTO-NCA (35%). A chromosomal aberration was detected in 11 patients (28%) by karyotyping, FISH or WGA. Of these, five patients had Turner syndrome (caused by a 45,X karyotype in four patients and by a deletion Xp11.23 in one patient). Five patients had a de novo microdeletion in chromosome band 2q24.3q32.1, 3q29, 6p25.5, 15q11.2 and 22q11.2, respectively, and one patient had a mosaic extra ring chromosome 7 (mos 47,XX, r(7)(p22q32)).

A disorder with mendelian inheritance was found in three patients (CHARGE syndrome in two patients, confirmed by mutations in CHD7 and Coffin Siris syndrome in one patient). Clinical details and results of karyotyping, FISH and WGA of these patients are shown in the online supplementary data.

Family history before cardiac screening of first-degree relatives

Before cardiac screening of the first-degree relatives, the three-generation family history was negative for congenital heart defects in 93 families (93/142, 65%), whereas in 49/142 (35%) it was positive for heart defects—namely, LVOTO in 24/142 families (17%) or for congenital heart defects other than LVOTO in 25 families (18%). In 10 of these 49 families the relative previously diagnosed with a heart defect was a parent or sibling.

Cardiac screening of first-degree relatives

Results of cardiac evaluation were abnormal in one or more first-degree relatives in 28/142 families (20%). Cardiac evaluation data were available for 449 of the 483 first-degree relatives (93%): 262/284 parents, (133 fathers, 129 mothers), 187/199 siblings (106 male, 81 female). Reasons for missing data in 34 relatives were: single-parent families, inability to cooperate (in young siblings), ‘not wanting to know’ and missed appointments. Of the 449 first-degree relatives tested, 34 (8%)...
were diagnosed with a cardiac anomaly (22/262 parents (8%), 12/187 siblings (6%)). The diagnoses of the affected first-degree relatives in these 28 families are listed in table 1. Of the 25 aortic valve anomalies, 20 were bicuspid, 3 tricuspid.

In 22 families one first-degree relative was affected, whereas in six families two first-degree relatives were affected. Eight affected siblings of index patients, in six separate families, did not have an affected parent.

In 12 of the 28 families (43%) the three-generation family history was completely negative before the screening, while in 10 families a first-degree relative (five siblings, five parents) was known to be affected, and in six families a further degree relative was affected. The cumulative result of family history and cardiac screening was positive in 61/142 (43%) of the families.

Twenty-four cardiac abnormalities in first-degree relatives (24/34, 71%) were new findings from our cardiac screening programme; the other 10 were already known before this study. One newly diagnosed relative showed dilatation of the aortic root (>40 mm), without a BAV. In one more father an aortic root of 40 mm was detected, which is borderline and will have to be followed up. The cardiac anomalies of the index patients (probands) in these 28 families were found in all LVOTO diagnoses (table 2), though BAV and HLHS showed higher prevalence in relatives than COA.

**DISCUSSION**

In a large cohort of 142 consecutive patients with LVOTO without NCA we showed that in 20% of the index patients a cardiac anomaly was present in one or more of their first-degree relatives. This was most frequently a BAV and in 71% of the affected first-degree relatives the cardiac anomaly had not been previously identified. In 12 (43%) of these 28 multiplex families the three-generation family history before ultrasound screening of the first-degree relatives was completely negative. NCA were present in 22% of the LVOTO index patients. Eleven patients had numerical chromosomal aberrations (5/11 were ‘Turner’s syndrome’) and these were likely to be causative because they were all newly arisen in the patients and have been previously described in association with heart defects. Details are provided in the online supplementary data. In a previous study on congenital heart disease, a high prevalence of aberrations was also found by array comparative genome hybridisation in selected patients. Our data show that a thorough clinical evaluation of NCA in patients with LVOTO is important, since a genetic cause can be detected in 35% of these patients.

In this study we restricted the use of WGA to the syndromic cases. Whether the non-syndromic patients also have chromosomal aberrations we do not know. Therefore, we cannot give an estimation of chromosomal aberrations in all patients with LVOTO. Erdogan et al showed that in non-syndromic patients with heart defects chromosomal aberrations may also be detected. However, the occurrence of these chromosomal aberrations is much lower (18/105 (17%)) than the frequency found in our patients with heart defects in combination with NCA (17% vs 35%). Furthermore, whether all these aberrations described by Erdogan are pathogenic is unclear as only three of the 18 were de novo, and only four were previously described as the cause of congenital malformations. Therefore, WGA in non-syndromic patients may reveal new loci for congenital heart diseases in the future, but the yield will be lower than in patients with NCA and the interpretation of pathogenicity will remain a challenge for scientists and clinicians.

The data of this study cannot be compared directly with those of previous studies on the occurrence of cardiac anomalies in relatives of patients with LVOTO because of differences in patient selection and methods. In our opinion, the number of affected families is more relevant than the number of affected relatives, because this reflects the heredity of the disease and bias due to ascertainment of large, affected families is avoided. However, in order to be able to compare our results with previous studies, we adjusted data derived from other studies to the format used in this study, if adequate information was provided. These adjusted data are presented in table 3.
In our study, 34 first-degree relatives (8%) had a cardiac anomaly and 20% of the index patients had an affected first-degree relative. Our results are in contrast with a population-based study detecting 15 cases of LVOTO in 1655 first-degree relatives of patients with LVOTO (prevalence 0.79%; RR = 12.9). However, this study was not designed to detect asymptomatic cardiac anomalies by cardiac ultrasound. Moreover, information about the number of families was not provided. Recent studies, using cardiac ultrasound screening, show higher prevalences in first-degree relatives than our findings, ranging from 12% to 18% of first-degree relatives and from 57% to 55% of the families. These high numbers, using comparable screening methods including echocardiography, probably confirm the selection bias in these studies due to selection of the most heritable subgroups (BAV and HLHS) and, more importantly, to selection towards familial disease in studies with non-consecutive patients.

Table 2  Affected relatives in 28 affected families

<table>
<thead>
<tr>
<th>Diagnosis in proband</th>
<th>Affected fathers</th>
<th>Affected mothers</th>
<th>Affected brothers</th>
<th>Affected sisters</th>
<th>Affected families (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAV/AVS</td>
<td>10</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>14/50 (28)</td>
</tr>
<tr>
<td>COA</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>10/78 (13)</td>
</tr>
<tr>
<td>HLHS</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>4/13 (31)</td>
</tr>
<tr>
<td>other</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0/1 (0)</td>
</tr>
<tr>
<td>total</td>
<td>15</td>
<td>7</td>
<td>5</td>
<td>7</td>
<td>28/142 (20)</td>
</tr>
</tbody>
</table>

AVS, aortic valve stenosis; BAV, bicuspid aortic valve; COA, coarctation of the aorta; HLHS, hypoplastic left heart syndrome

BAV was the most prevalent cardiac anomaly seen in asymptomatic relatives in our study, which is consistent with the results of previous studies. As nicely described in a review paper by Braverman, most individuals with a BAV will develop a complication during their life, these complications are often unsuspected and may result in sudden cardiac death. Most recent studies focus on the progressive dilatation of the aortic root, which may lead to aneurysm and dissection. Even in children, dilatation of the aortic root may be progressive: in 50% of the children a size of more than two SDs above the mean is reached 5 years after diagnosis. Interestingly, Biner et al found an increased risk of dilatation of the aortic root without a BAV in first-degree relatives of patients with a BAV, which is in line with our observation of one relative with dilated aortic root without a BAV and one relative with a borderline value. These studies emphasise that a BAV is not a harmless natural variant, but that it is associated with serious health risks. If patients at risk are identified, aortic dilatation may be postponed by prescription of β blockers and sudden unsuspected cardiac death may be prevented by timely surgical intervention.

The findings of this study, in our opinion suggest that the diagnostic strategy in patients with LVOTO should include: (a) a thorough clinical examination of the patient focused on NCA. If NCA are detected and no syndrome with known mendelian inheritance is recognised, karyotyping, FISH and/or WGA are advised since it reveals abnormalities in 28% of the LVOTO-NCA patients; (b) offering genetic counselling and cardiac screening to first-degree relatives of patients with LVOTO without NCA, because of the high occurrence of cardiac anomalies, often not previously recognised, in those relatives (20% of the families). The yield of this strategy in our study population is summarised in figure 3.

The limitations of this study are that we do not have follow-up data on the screened population of first-degree relatives. Therefore, we do not know whether interventions have occurred and whether these have prevented serious complications in this population. The economic impact and cost-effectiveness of our proposed strategy (cardiac screening of an average of three relatives per proband) cannot yet be judged. Another limitation is that our cohort of index patients also contains patients in follow-up and therefore may be under-representing HLHS.

Table 3  Studies on first-degree relatives of non-syndromic patients with LVOTO

<table>
<thead>
<tr>
<th>Studies</th>
<th>Index patients</th>
<th>Affected families/ families tested (%)</th>
<th>Affected first-degree relatives/first-degree relatives tested (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brenner 1989</td>
<td>11</td>
<td>No data provided</td>
<td>5/41 (12)</td>
</tr>
<tr>
<td>HLHS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huntington 1997</td>
<td>30</td>
<td>11/30 (37)</td>
<td>27/186 (15)</td>
</tr>
<tr>
<td>Adult BAV from ultrasound register</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loffredo 2004</td>
<td>84</td>
<td>No data provided</td>
<td>42/305 (14)</td>
</tr>
<tr>
<td>diagnosed 1990–1993</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cripe 2004</td>
<td>50</td>
<td>23/50 (46)</td>
<td>No data provided</td>
</tr>
<tr>
<td>BAV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levin 2004</td>
<td>113</td>
<td>42/113 (37)</td>
<td>45/278 (16)</td>
</tr>
<tr>
<td>25 AVS, 3 BAV, 52</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COA, 38 HLHS, 2 other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McBride 2005</td>
<td>124</td>
<td>No data provided</td>
<td>25/329 (8)</td>
</tr>
<tr>
<td>34 AVS, 1 BAV, 59</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDA, 30 HLHS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hinton 2007</td>
<td>38</td>
<td>21/38 (55)</td>
<td>23/126 (18)</td>
</tr>
<tr>
<td>38 HLHS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>This study</td>
<td>142</td>
<td>28/142 (20)</td>
<td>34/449 (8)</td>
</tr>
<tr>
<td>50 BAV/AVS, 78</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDA, 13 HLHS, 1 other</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data calculated from the referenced papers.

113/124 index patients in the McBride study are the same as those in the Lewin study. AVS, aortic valve stenosis; BAV, bicuspid aortic valve; COA, coarctation of the aorta; HLHS, hypoplastic left heart syndrome; LVOTO, left ventricular outflow tract obstruction.

Figure 3  Diagnostic strategy for patients with LVOTO. LVOTO, left ventricular outflow tract obstruction (for definition see text); NCA, non-cardiac congenital anomalies; WGA, whole genome array—comparative genomic hybridisation.

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owing to the high mortality in this group. If heredity in this most severe group is higher than average, the number of affected families may be underestimated in our cohort. Another limitation of this study is that we do not yet have complete data on NOTCH1 mutation screening in this cohort; this will be part of future research. An obvious limitation of this study, even though we included consecutive patients, is that the possibility of some bias towards syndromic and familial cases, caused by stronger motivation to consent in these families, cannot be ruled out.

We conclude that first-degree relatives of patients with LVOTO have a high prevalence of asymptomatic cardiac anomalies. These are most frequently BAV, and thus relatives of patients with LVOTO carry a risk of serious complications, including sudden cardiac death, which may be preventable. Therefore, offering genetic counselling and cardiac screening including echocardiography, to all families of patients with LVOTO is warranted.

Future research should focus on finding the genes responsible for familial LVOTO, so that all affected relatives can be easily tracked, especially those with asymptomatic BAV who are at risk of preventable sudden cardiac death.

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Competing interests None.

Ethics approval Ethics Approval from the UMCG ethics committee.

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CORRESPONDENCE

Syncope following ‘pill-in-the-pocket’ treatment of atrial fibrillation with propafenone plus quinidine

To the Editor The important report by Alboni et al., not only documents risks associated with the use of propafenone during ‘pill-in-the-pocket’ (PIP) therapy for paroxysmal atrial fibrillation (PAF) but also hints at techniques by which its use may be made safer. The primary metabolism of propafenone occurs through hepatic CYP4502D6 isoenzyme activity, resulting in differences between the safety of propafenone administered intravenously and orally. CYP2D6 activity may also be strongly inhibited by other commonly prescribed medications, including quinidine, amiodarone, cimetine, erythromycin and most selective serotonin re-uptake inhibitor antidepressants, whose concurrent use can be expected to increase both their own concentrations and that of propafenone. One hundred milligrams of oral quinidine administered twice daily increases blood levels of propafenone by 300%, increasing its anti-arrhythmic and pro-arrhythmia potentials. Hepatic CYP2D6 activity also decreases 50% with advancing age, requiring both patient ages and their concurrent medication use to be included in anticipating propafenone-associated pro-arrhythmias.

The frequency of PAF is four to five times higher in middle-aged men with a long history of endurance sports activity than in other men of similar age, with an associated increased potential among them for drug-induced pro-arrhythmias suspected.

We recently observed an 81-year-old general internist–distance runner with no underlying cardiovascular disease and 24 years of successfully treating 100 episodes of PAF with PIP quinidine, who ingested his first lifetime 150 mg propafenone tablet following failure of three 324 mg tablets of quinidine gluconate to induce conversion over 6 h. Two hours after propafenone ingestion, he converted to sinus rhythm but fainted 2 h after conversion and was oriented and conversant 3 min later with a regular pulse at 62 beats per minute but unable to sit upright because of lightheadedness. Twenty minutes after syncope, normal sinus rhythm and a blood pressure of 60/42 were documented. He received intravenous saline, remained in normal sinus rhythm and, 2 h later, felt well, his pattern thought to represent myocardial stunning following an arrhythmia induced by his quinidine–propafenone combination. Subsequently, he has competed two marathons and easily converted 12 episodes of PAF with PIP quinidine.

We are unaware of other endurance athletes with PAF who receive PIP therapy or other patients with PAF who have successfully used single-medication PIP therapy for several decades without complication. Our observations suggest that oral propafenone may be inappropriate for treatment of PAF in endurance athletes and in patients consuming other drugs which use CYP2D6 metabolism, and that quinidine therapy might be appropriate for PIP treatment under some circumstances.

We share both the opinion of Alboni and his group that PIP therapy may be greatly underused and their enthusiasm for further exploration of its benefits and risks.

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CORRECTIONS

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This paper was erroneously published under the section heading ‘Cardiomyopathy’. It should have been ‘Congenital heart disease’. The journal apologises for this error.

doi:10.1136/hrt.2009.190744corr1


There are errors in table 1 of this paper. The term ‘Mean Power (kJ)’ should be replaced by ‘Mean Work Done (kJ)’. Also, the numbers for this variable should be corrected, as there was an error in the formula used. The corrected variable name and the results appear in the table published below. The corrected results are similar in terms of the effect of passive smoking since they are heavily dependent on the cycle resistance (because the rpm were stable at 60) and, as such, the error was systematic across all time points. Therefore, the main findings and the conclusions of the paper remain the same and the only part that requires amendment is the magnitude of the numbers in this variable.

doi:10.1136/hrt.2004.055731corr1


Corrections doi:10.1136/hrt.2010.211433corr1

Table 1 Mean ± SD of cardiopulmonary variables for men and women for the statistically significant post-hoc comparisons

<table>
<thead>
<tr>
<th>Variable</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean work done (kJ)</td>
<td>242.4 ± 61.1†</td>
<td>135.6 ± 41.2‡</td>
<td>147.6 ± 71.4†</td>
<td>138.0 ± 64.5‡</td>
</tr>
<tr>
<td>Mean work done (kJ)</td>
<td>159.0 ± 38.3‡</td>
<td>84.8 ± 26.6*§</td>
<td>103.9 ± 25.3†</td>
<td>100.1 ± 22.9†</td>
</tr>
</tbody>
</table>

*Statistically significant (p<0.05) difference between sexes for the same measurement.
†Statistically significant (p<0.05) difference from previous time.
‡Statistically significant (p<0.05) difference of T0 from T1.