Abstract

Background: Tissues that depend on aerobic energy metabolism suffer most in diseases caused by mutations in mitochondrial DNA (mtDNA). Cardiac abnormalities have been described in many cases, but their frequency and clinical spectrum among patients with mtDNA mutations is unknown.

Methods: Thirty-nine patients with the 3243A>G mtDNA mutation were examined, methods used included clinical evaluation, electrocardiogram, Holter recording and echocardiography. Autopsy reports on 17 deceased subjects were also reviewed. The degree of 3243A>G mutation heteroplasmy was determined using an Apa I restriction fragment analysis. Better hearing level (BEHL0.5–4 kHz) was used as a measure of the clinical severity of disease.

Results: Left ventricular hypertrophy (LVH) was diagnosed in 19 patients (56%) by echocardiography and in six controls (15%) giving an odds ratio of 7.5 (95% confidence interval; 1.74–67). The dimensions of the left ventricle suggested a concentric hypertrophy. Left ventricular systolic or diastolic dysfunction was observed in 11 patients. Holter recording revealed frequent ventricular extrasystoles (>10/h) in five patients. Patients with LVH differed significantly from those without LVH in BEHL0.5–4 kHz, whereas the contribution of age or the degree of the mutant heteroplasmy in skeletal muscle to the risk of LVH was less remarkable.

Conclusions: Structural and functional abnormalities of the heart were common in patients with 3243A>G. The risk of LVH was related to the clinical severity of the phenotype, and to a lesser degree to age, suggesting that patients presenting with any symptoms from the mutation should also be evaluated for cardiac abnormalities.

Background

Mitochondrial diseases form a heterogeneous group of disorders with defects in mitochondrial oxidative phosphorylation. The majority of these diseases is caused by
mutations in mitochondrial DNA (mtDNA) [1]. MtDNA encodes 13 out of more than 80 polypeptides in the mitochondrial respiratory chain complexes, and the ribosomal RNA and transfer RNA necessary for translation in mitochondria [2]. The clinical variability of these disorders is partly due to the fact that all organs may be affected, although those with a high energy expenditure suffer most, e.g. brain, skeletal muscle and cardiac muscle. Furthermore, the mutant genome may coexist with the wild-type genome, and the degree of this heteroplasmy partly determines the clinical phenotype as those organs with a high proportion of the mutant genome tend to be more severely affected [3].

Cardiomyopathy is one of the clinical phenotypes associated with mtDNA mutations [4–7]. Patients with mtDNA deletions, presenting with the phenotype of the Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia or the Pearson’s syndrome, often develop conduction defects [6], but dilated cardiomyopathy leading to heart failure has also occasionally been reported [8]. Several point mutations of mtDNA have been described in patients with cardiomyopathy including mutations in the genes coding for tRNA^{Leu}[4,5], tRNA^{Ile}[9], tRNA^{Lys}[6], tRNA^{Glu}[10], 12S rRNA [11] and certain structural genes [7]. Most commonly, the cardiomyopathy associated with these mutations is hypertrophic. In addition, multiple mtDNA deletions with autosomal dominant inheritance may present with cardiomyopathy [12].

Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) is a distinct clinical syndrome characterized by short stature, seizures, hemiparesis, hemianopia and cortical blindness [13]. The syndrome is genetically heterogenous, but approximately 80% of the patients with the MELAS syndrome harbor a heteroplasmic A-to-G transition in the tRNA^{Leu} at base pair 3243 in mtDNA (3243A>G) [14]. Cardiomyopathy has been described in patients with the 3243A>G mutation [5,6,15], but the frequency and the degree of severity of the cardiac manifestations has remained obscure as the earlier reports have been based on studies of small number of selected patients. Therefore, we set out to search for the frequency and quality of cardiac abnormalities among 52 members from 13 families with the 3243A>G mutation. The families have been ascertained in the population of the province of Central Ostrobothnia. Persons that had reached the age of 18 years and belonged to the sibship of the proband or to the sibship of proband’s mother were considered for the study. Eligible persons had been shown to be carriers of 3243A>G mutation or were first-degree maternal relatives to a verified mutation carrier. The latter persons are considered obligatory carriers of the mutation and they harbor the mutation with a high probability [17]. Cardiological evaluation was performed on 35 verified 3243A>G carriers and 13 verified or obligatory carriers were studied by review of autopsy reports. Both clinical data and autopsy data were available from four additional subjects with the 3243A>G mutation. Better ear hearing level (BEHL0.5–4 kHz), calculated as the mean of the hearing levels over the frequencies of 0.5, 1, 2 and 4 kHz, was used as a measure of the clinical severity of disease caused by 3243A>G [18]. Twenty patients had diabetes mellitus that was considered to be caused by the 3243A>G mutation in each case. A causal relationship was assumed if three of the following four criteria were fulfilled: progressive insulin secretory defect, lack of islet cell antibodies, low body mass index and onset at early adulthood [19].

**Controls**

Each patient with 3243A>G mutation was matched with respect to age, sex and diagnosis of hypertension with a control that was chosen from a population-based cohort of 1200 persons. This cohort includes 600 patients with an anti-hypertensive medication and 600 nonhypertensive subjects [20]. For 14 patients with 3243A>G mutation that were under 40 years old, a matched control was chosen from echocardiographic registry at the Cardiologic Department in Oulu University Hospital. The controls had been examined because of palpitation, short of breath or suspicion of genetic aortic disease and after cardiological evaluation they had been deemed healthy. Diabetes is a common phenotype associated with the 3243A>G mutation and presents with features that differ from those in type I and type II diabetes mellitus [19]. Therefore, matching of cases and controls with respect to diabetes mellitus was not attempted.

The study was approved by the Ethical Committee of the Medical Faculty at the University of Oulu and the clinical examinations were carried out with the informed consent from the patient.

**Cardiac examinations**

Twelve-lead ECGs were obtained in 39 patients, and these were interpreted according to standard criteria. Left ventricular hypertrophy (LVH) was diagnosed, whenever R in V₅ or V₆ + S in V₁ exceeded 4.5 mV [21]. Echocardiography was performed in 35 patients, and the measurements were obtained and interpreted according to the standards.

**Methods**

**Patients**

We have previously ascertained 11 pedigrees with the 3243A>G mutation in the population of the province of Northern Ostrobothnia in Finland [16] and two additional pedigrees have been ascertained in the population of the province of Central Ostrobothnia. Persons that had reached the age of 18 years and belonged to the sibship of the proband or to the sibship of proband’s mother were considered for the study. Eligible persons had been shown to be carriers of 3243A>G mutation or were first-degree maternal relatives to a verified mutation carrier. The latter persons are considered obligatory carriers of the mutation and they harbor the mutation with a high probability [17]. Cardiological evaluation was performed on 35 verified 3243A>G carriers and 13 verified or obligatory carriers were studied by review of autopsy reports. Both clinical data and autopsy data were available from four additional subjects with the 3243A>G mutation. Better ear hearing level (BEHL0.5–4 kHz), calculated as the mean of the hearing levels over the frequencies of 0.5, 1, 2 and 4 kHz, was used as a measure of the clinical severity of disease caused by 3243A>G [18]. Twenty patients had diabetes mellitus that was considered to be caused by the 3243A>G mutation in each case. A causal relationship was assumed if three of the following four criteria were fulfilled: progressive insulin secretory defect, lack of islet cell antibodies, low body mass index and onset at early adulthood [19].

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of the American Society of Echocardiography (ASE) [22]. The left ventricular volumes and ejection fraction were calculated using the method of Teichholz. Left ventricular function was evaluated using also 2-dimensional echocardiography and visual interpretation. LVH was diagnosed by left ventricular wall thickness when interventricular or posterior wall diastolic thickness exceeded 12 mm in non-hypertensive and 14 mm in hypertensive patients [23]. Left ventricular mass (LVM) was calculated from the ASE measurements according to the corrected equation [24] and it was related to body surface area. The cut-off points for left ventricular hypertrophy by left ventricular mass-index (LVMI) were 134 g/m² for men and 110 g/m² for women [25]. The mitral inflow velocity was measured by pulsed-wave Doppler echocardiography in the apical four-chamber view. Peak early diastolic and peak late diastolic velocities were measured and E/A max ratios were used when evaluating diastolic function of the left ventricle. Regurgitation of valves was estimated with pulsed-wave or color Doppler echocardiography.

Thirty-six patients underwent standard 24-hour Holter monitoring. Four patients were catheterized, one for chest pain and LVH, one for congestive cardiomyopathy, one for LVH and unexpected pulmonary oedema and one for asymptomatic paroxysmal Mobitz type II AV-block observed during the Holter monitoring.

Review of autopsy reports
Autopsy had been performed on 17 cases and the weight of the heart had been documented in 12 autopsies. In the remaining reports the heart was stated to be normal in size in four cases and in one report the heart was described as hypertrophic. Body length was recorded in all autopsy reports. In none of the autopsies chamber partition had been made, but the total heart weight is known to provide a good approximation of left ventricular hypertrophy [26]. Cardiac hypertrophy was diagnosed if the heart weight of the patient was one standard deviation greater than the mean weight of the normal heart stratified by sex and body length [27].

Mitochondrial DNA analysis
Muscle biopsy specimens were obtained from 33 patients with 3243A>G from the anterior tibial muscle or vastus lateralis of the quadriceps muscle, right ventricular endomyocardial biopsies were obtained from four patients during catheterisation, and myocardial samples were obtained from six patients at autopsy. Total DNA was isolated from tissue samples by the standard SDS-proteinase K method. The 3243A>G mutation was determined using an Apa I restriction digestion of a 390 bp mtDNA fragment (from nt 3150 to nt 3550) amplified by PCR in the presence of 35S-ATP [28]. The fragments were electrophoresed through a 6% non-denaturing polyacrylamide gel, which was then dried and autoradiographed at -72°C overnight using Kodak XAR film with an intensifying screen. Films were analyzed with a Bioimage scanner and image processing apparatus (Millipore, Ann Arbor, MI).

Statistical analysis
The Mann-Whitney U test was used to detect difference between two groups and Kruskall-Wallis test between several groups. The Wilcoxon signed rank test and the McNemar test were used when comparing paired data.

Results
Clinical features of the patients
Thirty-nine patients with the 3243A>G mutation (15 men, 24 women; mean age 48 ± 13 years) were clinically studied for cardiac abnormalities. Twenty of them were diabetic, but none of them had diabetic nephropathy. The cardiovascular history was uneventful in 27 patients, while the remaining patients reported chest pain (n = 7), hypertension (n = 7), coronary artery disease (n = 6) that had required by-pass surgery in two patients and dyspnea (n = 5). The physical examination was normal in most patients, but auscultation revealed systolic murmurs in five and gallops in three patients. Elevated central venous pressure was observed in two patients. Resting ECG revealed conduction abnormalities in five patients (abnormally short PQ time, 2; 1° AV block, 1; bundle branch blocks, 2). Two patients had sinustachycardia at rest with heart rate exceeding 100 bpm.

Left ventricular hypertrophy
Echocardiography was performed on 34 patients with 3243A>G and 34 controls that were matched with respect to age, sex and the diagnosis of hypertension (Table 1). Echocardiography revealed an increased ventricular wall thickness suggesting LVH in 19 patients (56%; 95% confidence interval (CI); 38 – 73%) and in six controls (15%; 95% CI; 6 – 31%) giving an odds ratio of 7.5 (95% CI; 1.74 – 67). The median left ventricular septal or posterior wall end-diastolic thickness was 14 mm (range 12 – 23 mm) in the patients with LVH (Table 1). The thickness of the left ventricular septum and posterior wall was significantly greater in the patients than in the controls suggesting concentric hypertrophy (Table 1). Systolic dysfunction was diagnosed in four patients with LVH, whereas abnormal left ventricular filling patterns and thus signs of diastolic dysfunction were observed in five patients (Table 2).

The ratio of left ventricular mass to body surface area (LVMI) could be calculated for 28 patients with the 3243A>G mutation. The mean LVMI was slightly but not significantly higher in the patients than in the controls. If cut-off points over 134 g/m² for men and 110 g/m² for women
were used to diagnose left ventricular hypertrophy, the patients with the 3243A>G mutation had significantly more LVH than the controls (Table 1).

Thirty-two members in the sibships had died and an autopsy had been performed on 17 of them including four patients that had been examined clinically during life. The review of the autopsy reports revealed nine patients with LVH giving a frequency of 53%. The median heart weight in these patients was 472 g (range 322 – 570 g). Altogether, we found 26 patients with LVH among the 47 patients studied suggesting a total frequency of 55% (95% CI; 40 – 69%) for LVH in the clinical study cohort and the autopsy cohort.

Factors contributing to cardiac hypertrophy
There was no difference in sex distribution or frequency of diabetes mellitus between the patients with LVH and patients without LVH. The mean age of the patients with LVH was slightly higher than that of the patients without LVH (Table 3) and a contribution of age was also suggested by autopsy data as the mean age at death of the patients with LVH, $59 \pm 15$ years, was significantly higher than the age, $38 \pm 10$ years, of the patients that died without LVH ($p = 0.004$). The severity of disease measured by BEHL0.5–4 kHz was significantly higher among patients with LVH.

The degree of the 3243A>G mutation heteroplasmy was determined in skeletal muscle of 33 out of the 39 patients

| Table 1: Comparison of the patients with the 3243A>G mutation and the matched controls. |
|--------------------------------|--------------------------------|----------------|
| Patients with 3243A>G | Controls | p-value |
|----------------------|----------|---------|
| Gender (% men) | 38.5 | 38.5 | 1.00 |
| Age (yrs) | $46.7 \pm 12.7$ | $46.8 \pm 11.5$ | 0.63 |
| Hypertension (n) | 10 | 10 | 1.00 |
| Diabetes mellitus (n) | 20 | 7 | 0.001 |
| **Left ventricular dimensions** | | |
| ST(D) (mm) | $12.2 \pm 3.2$ | $10.0 \pm 1.7$ | 0.003 |
| PWT(D) (mm) | $12.1 \pm 3.7$ | $10.0 \pm 1.8$ | 0.02 |
| LVD(D) (mm) | $43.4 \pm 5.8$ | $49.6 \pm 5.4$ | <0.001 |
| LVH* (n) | 19 | 6 | 0.002 |
| **Left ventricular mass** | | |
| LVMI (g/m²) | $127 \pm 54$ | $102 \pm 24$ | 0.06 |
| LVH† (n) | 12 | 3 | 0.02 |

ST(D), thickness of interventricular septum in diastole; PWT(D), thickness of posterior ventricular wall in diastole; LVD(D), left ventricular end-diastolic diameter; LVH*, left ventricular hypertrophy = septal or posterior wall end-diastolic thickness ≥ 12 mm in non-hypertensives and ≥ 14 mm in medically treated hypertensives [23]; LVMI, left ventricular mass/body surface area, where LVM is left ventricular mass calculated by the method of American Society of Echocardiography: $0.8 \times (1.04 \times ((LVID/10 + IVS/10 + PVW/10)^3 – (LVID/10)^3) + 0.6$ [24,25]; LVH†, left ventricular hypertrophy = LVMI over 134 g/m² for men and 110 g/m² for women [25]. Values are means ± standard deviations.

| Table 2: Findings at cardiac examination of the patients with the 3243A>G mutation. |
|--------------------------------|--------------------------|
| Patients (n) | |
| **ECG** | |
| Normal | 22 |
| LVH | 9 |
| Conduction disturbances | 5 |
| Other | 9 |
| **Echocardiography** | |
| Normal | 16 |
| LVH | 19 |
| LVSD or LVDD | 9 |
| Valvular disorders | 6 |
| **Holter-recordings** | |
| Normal | 14 |
| Benign extrasystoles† | 15 |
| VES >30/h | 1 |
| SVT/AF attacks | 4 |
| NSVT | 1 |
| Conduction disturbances‡ | 4 |

LVH, left ventricular hypertrophy; LVSD, left ventricular systolic dysfunction; LVDD, left ventricular diastolic dysfunction; VES, ventricular extrasystoles; SVT, supraventricular tachycardia; AF, atrial fibrillation; NSVT, non-sustained ventricular tachycardia. LVSD was diagnosed if ejection fraction < 50%. LVDD was diagnosed if E/A-ratio < 1. Other ECG findings include: Q-wave abnormalities, 2; ST/T-wave abnormalities, 4; sinus tachycardia, 2; prolonged QTc, 1; Supraventricular extrasystoles or VES <30/h. Conduction disturbances include: Mobitz II AV-block, 1; intermittent delta wave, 1; sinus arrests (2.4–2.8 s), 2.

Factors contributing to cardiac hypertrophy
There was no difference in sex distribution or frequency of diabetes mellitus between the patients with LVH and patients without LVH. The mean age of the patients with LVH was slightly higher than that of the patients without LVH (Table 3) and a contribution of age was also suggested by autopsy data as the mean age at death of the patients with LVH, $59 \pm 15$ years, was significantly higher than the age, $38 \pm 10$ years, of the patients that died without LVH ($p = 0.004$). The severity of disease measured by BEHL0.5–4 kHz was significantly higher among patients with LVH.

Three patients had suffered from stroke-like episodes, two of whom had LVH.
that were clinically examined. The degree of the mutant heteroplasmy did not differ between patients with LVH and patients without LVH, but among the patients with LVH we found a linear correlation between the degree of the mutant heteroplasmy and LVMI (Pearson correlation coefficient 0.641, p = 0.034). Furthermore, the degree of the mutant heteroplasmy was 81% (range; 72 – 89%) in endomyocardial samples from four patients, two of whom were diagnosed with LVH, and 75% (range; 57 – 81%) in cardiac muscle samples obtained at autopsy from six patients, three of whom had LVH. Samples from both skeletal muscle and endomyocardium or postmortem myocardium were available from seven patients. The mean degree of the heteroplasmy of the 3243A>G mutation in the skeletal muscle was 78\(\pm\)7% and that in cardiac muscle 81\(\pm\)7% (p = 0.40; Wilcoxon test).

**Arrhythmias and conduction disturbances**

Holter monitoring was accomplished in 36 patients. Clinically significant arrhythmias or conduction disturbances were found in 10 patients suggesting a frequency of 28% (Table 2). Five patients presented with \(>\) 10 ventricular extrasystoles/hour. The highest frequency of ventricular extrasystoles (2700/24 hours) with episodes of bigeminy and trigeminy was observed in the only patient with congestive cardiomyopathy. Episodes of non-sustained ventricular tachycardia were observed in one patient with LVH but only one patient with congestive cardiomyopathy without LVH in the clinical study and one patient with cardiac dilatation in the review of the autopsy reports. Interestingly, knock-out mice with inactivated mitochondrial adenine nucleotide translocator develop hypertrophic cardiomyopathy [29] suggesting that cytoplasmic ATP deficiency is an essential contributor to the pathogenesis of this condition. Indeed, a role for ATP deficiency in patients with 3243A>G can be further inferred from studies on cultured myoblasts harboring the 3243A>G mutation [30]. On the other hand, dilated cardiomyopathy develops in mutant mice lacking manganese superoxide dismutase [31] suggesting that the increased oxidative stress may have a role in the pathogenesis of this condition. However, the pathogenetic cascade in cardiomyopathy may also include other events related to mitochondria, such as disturbance of calcium homeostasis or apoptosis.

**Discussion**

Our extensive screening of a defined population in northern Finland for the 3243A>G mtDNA mutation has yielded a good approximation of a population-based cohort of patients with this mutation [16]. In the present study we examined complete sibships from 11 pedigrees ascertained in the screening as well as two additional pedigrees from a neighboring province, where the prevalence of the mutation appears to be similar to that observed in the original ascertainment population. We found that LVH was the most common cardiac abnormality in pedigrees with the 3243A>G mtDNA mutation. LVH was diagnosed in 19 out of 34 patients by echocardiography and in nine out of 17 patients in autopsy suggesting an overall frequency of 55% among verified or obligatory carriers of the mutation. Furthermore, comparison of the patients with the 3243A>G mutation with matched controls revealed that the odds ratio of LVH was 7.5.

Clinically defined cardiomyopathy has been reported among patients with various other mtDNA point mutations and these case reports suggest that LVH is more common than cardiac dilatation in mitochondrial diseases [7]. We found that the 3243A>G mutation was almost exclusively associated with LVH, as we observed 26 patients with LVH but only one patient with congestive cardiomyopathy without LVH in the clinical study and one patient with cardiac dilatation in the review of the autopsy reports. LVH was diagnosed if septal or posterior wall end-diastolic thickness \(\geq\) 12 mm in non-hypertensives and \(\geq\) 14 mm in medically treated hypertensives [23]. BEHL\(_{0.5-4\text{kHz}}\), better ear hearing level over the frequencies 0.5 kHz, 1 kHz, 2 kHz and 4 kHz. The values are medians (range)

|                  | Patients with LVH | Patients without LVH | p Value |
|------------------|-------------------|----------------------|---------|
| Men/women (n)    | 9/10              | 6/14                 | 0.33    |
| Age (years)      | 53 (26 – 69)      | 45 (22 – 65)         | 0.28    |
| Mutant heteroplasmy in muscle (%) | 73 (48 – 83) | 64 (30 – 91) | 0.34 |
| BEHL\(_{0.5-4\text{kHz}}\) (dB) | 53 (0 – 103) | 29 (0 – 64) | 0.022 |

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plete AV conduction block [32]. We found some patients with abnormalities in impulse formation or conduction, and most often these were associated with LVH. An intermittent delta wave suggesting pre-excitation was found in one patient with LVH, an observation reported also earlier in patients with the 3243A>G mutation [33]. Many studies have clearly demonstrated that LVH is an important predictor of cardiovascular events and mortality [34]. LVH is a forerunner of coronary artery disease, cardiac failure, stroke and peripheral artery disease, and it is associated with ventricular arrhythmias potentially leading to sudden cardiac death even in the absence of clinically significant coronary artery disease [35]. We found functional abnormalities, defined as the presence of significant ventricular arrhythmias or left ventricular dysfunction, in the majority of the LVH patients. Therefore, cardiac evaluation of patients with 3243A>G seems worthwhile as an assessment of the risk of these lifethreatening events.

The relative amount of the mutant genome in tissues is one factor affecting the biochemical phenotype of mtDNA diseases, although nuclear modulatory factors, synergistic mtDNA mutations and mtDNA copy number may also contribute [36]. Furthermore, the clinical phenotype is modulated by an imbalance between the energy demand and energy supply of a given tissue and by environmental or physiological factors, such as aging [37]. We found that the risk of LVH was substantially increased among patients with the 3243A>G mutation compared to controls suggesting a role for the mutation itself. No contribution could be assigned to gender or diabetes mellitus, but higher age and more severe clinical phenotype were associated with the risk of LVH. Interestingly, there was no clear difference in the proportion of the mutant genome between patients with LVH and patients without LVH suggesting that estimation of the risk of LVH cannot solely be based on the degree of mutant heteroplasmy in muscle. However, among patients with LVH a significant correlation was observed between LVMI and the degree of the mutation heteroplasmy. We found that there was no difference in the degree of mutant heteroplasmy in skeletal and cardiac muscle suggesting that the degree of mutant heteroplasmy in skeletal muscle may be used as an estimate of that in the cardiac muscle.

The frequency of mtDNA mutations among unselected patients with hypertrophic or dilated cardiomyopathy is unknown. Although the 3243A>G mutation is probably the most common pathogenic mutation in mtDNA [16], and although the frequency of cardiomyopathy in patients with this mutation is fairly high, there are many other mtDNA mutations that have been reported to cause hypertrophic or dilated cardiomyopathy [38]. Many of these mutations cluster either in the gene for leucine(UUR)-tRNA or isoleucine-tRNA, but some mutations have been found in genes coding for the subunits of the respiratory chain. The clinical phenotypes caused by these mutations are very variable ranging from fatal infantile cardiomyopathy to mildly symptomatic adult onset cardiomyopathies. Most of these mutations have been detected only in single patients or families, and currently their significance in the clinical diagnostics is not known. However, the total frequency of various mtDNA mutations in patients with cardiomyopathy may be high enough to justify efforts for specific diagnosis, at least in patients with familial cardiomyopathy or with multiorgan syndrome involving cardiomyopathy.

Conclusion
Our results indicate that patients with the 3243A>G mtDNA mutation bear a considerable risk for cardiac pathology and, therefore, these patients should be evaluated for cardiac abnormalities, especially if other clinical manifestations from the mutation are present.

Competing interests
None declared.

Authors’ contributions
KM-V participated in the design of study, carried out the cardiac evaluation of the patients, performed the statistical analysis and drafted the manuscript.

KP participated in the design of study, carried out the cardiac evaluation of the patients and participated in the manuscript preparation.

M-LK participated in the design of study, carried out the cardiac evaluation of the patients and participated in the manuscript preparation.

IEH participated in the design of study and participated in the manuscript preparation.

KM participated in the design of study, carried out the cardiac evaluation of the patients, performed the statistical analysis and coordinated the study.

All authors read and approved the final manuscript.

Acknowledgements
The expert technical assistance of Ms. Anja Heikkinen is acknowledged. This study was supported in part by grants from the Finnish Foundation for Cardiovascular Research, from the Research Council for Health within the Academy of Finland and from the Sigrid Juselius Foundation.

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Pre-publication history
The pre-publication history for this paper can be accessed here:

http://www.biomedcentral.com/1471-2261/2/12/prepub