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Factors influencing outcome in patients with obstructive hypertrophic cardiomyopathy

Effects of pharmacotherapy, pacing and surgical myectomy

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av

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Avhandlingen baseras på följande delarbeten

I. Davood Javidgonbadi, Bert Andersson, Nils-Johan Abdon, Maria Schaufelberger, Ingegerd Östman-Smith. Factors influencing long-term heart failure mortality in patients with obstructive hypertrophic cardiomyopathy in Western Sweden: probable dose-related protection from beta-blocker therapy.
Open Heart 2019; 6:e000963. doi:10.1136/openhrt-2018-000963

II. Davood Javidgonbadi, Nils-Johan Abdon, Bert Andersson, Maria Schaufelberger, Ingegerd Östman-Smith. Short atrioventricular delay pacing therapy in young and old patients with hypertrophic obstructive cardiomyopathy: good long-term results and a low need for reinterventions.
Europace 2018;20:1683-1691(e-publication (2017) doi:10.1093/europace/eux331)

III. Davood Javidgonbadi, Maria Schaufelberger, Ingegerd Östman-Smith. Factors contributing to excess female mortality in hypertrophic obstructive cardiomyopathy.
Manuscript

IV. Davood Javidgonbadi, Bert Andersson, Nils-Johan Abdon, Ingegerd Östman-Smith. Morbidity and resource usage after myectomy or pacing-treatment in hypertrophic obstructive cardiomyopathy: a case-control study.
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Factors influencing outcome in patients with obstructive hypertrophic cardiomyopathy

Effects of pharmacotherapy, pacing and surgical myectomy

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ABSTRACT

Background: Most studies on risk factors for disease-related mortality in hypertrophic cardiomyopathy (HCM) have emanated from specialized tertiary centres which are subject to possible referral bias. About one quarter of HCM-patients have outflow obstruction in the left ventricle, hypertrophic obstructive cardiomyopathy (HOCM). Myectomy has been recommended as "gold standard" treatment for obstruction in American Heart Association (AHA) guidelines from 2011, and short atrio-ventricular delay pacing (pacing) is not considered. European Society of Cardiology Guidelines 2014 recommended pacing only to patients who are ≥65 years of age with co-morbidities. Therefore, it appeared appropriate to study the long-term outcome of patients with HOCM in complete geographical cohort in order to assess risk factors and survival of different therapies. **Methods**: In Paper I the total cohort of 251 HOCM patients (128 male, 123 female) with a mean follow-up of 14.4±8.9 years were studied for risk factors for disease-related mortality, and the effect of therapy (Conservative=no, or only medical, therapy n=121; pacing n=88; and myectomy n=42). In Paper II and IV we have compared the effect of pacing and myectomy on mortality (Paper II), and by a case-control methodology compared the complications and cost-effectiveness of those two methods (Paper IV). In Paper III we have studied the relationship between sex and risk-factors for disease-related death. **Results**: *Paper I*: There were 65 disease-related deaths. Risk-factors for disease-related death on multivariate Cox hazard regression were: female sex (p=0.005), age at diagnosis (p<0.001), outflow gradient ≥50 mm Hg at diagnosis (p=0.036) and at follow-up (p=0.001). Sudden cardiac death caused 17%, and heart failure 62%, of disease-related deaths. Late independent predictors of heart failure death were: female sex (p=0.003), outflow gradient ≥50 mm Hg at latest follow-up (p=0.032), verapamil/diltiazem therapy (p=0.012) and coexisting hypertension (p=0.031). Neither myectomy nor pacing modified survival, but early and maintained beta-blocker therapy was associated with dose-dependent reduction in disease-related death. Beta-blockers were used in 71.3% of patients from diagnosis. Kaplan-Meier survival curves analyzed in initial dose bands of 0-74, 75-149 and ≥150 mg metoprolol/day showed 10-year freedom from disease-related deaths of 83.1%, 90.7% and 97.0%, respectively (p-trend=0.00008). Even after successful relief of outflow obstruction by intervention, there was survival benefit of metoprolol doses ≥100 mg/day (p=0.01). *Paper II*: Post-intervention follow-up was 12.9±8.7 years and 12.2±5.0 years, in myectomy and pacing respectively. Both intervention treatments improved New York Heart Association (NYHA) class and outflow gradients significantly and equally, without survival inferiority for pacing (log-rank p=0.43). Survival after diagnosis was not different to that in patients only treated conservatively either (p=0.51 pacing/conservative; p=0.39 myectomy/conservative). Re-intervention in patients ≥18 years at procedure was needed due to return of the outflow gradient in 3.5% of paced vs 15.6% myectomy patients. Pacing therapy was equally effective in patients aged 13-64 years (n=44), as in patients ≥65 years (n=44). *Paper III*: At diagnosis the median age of females was 11 years higher than for men. Females had a higher disease-related mortality than males (log-rank, p=0.003). Excess female deaths were caused by chronic heart failure, Hazard ratio (HR) 3.76 [1.85-7.66; p=0.0003] in the age-matched group, and by myocardial infarctions (p=0.029). There was no sex-bias in respect to interventional procedures, but a lower proportion of females received beta-blocker therapy initially (64% versus 78%, p=0.011), and in a smaller dose (p=0.006). Verapamil/diltiazem was used in 17.1% females compared to 7.8% of males (p=0.034), and HR for heart failure deaths with verapamil/diltiazem therapy was 4.20 [1.72-10.23; p=0.002] in the age-matched groups of both sexes. *Paper IV*: There were fewer peri-procedural complications in the pacing-group compared to myectomy-group (3.2% in pacing and 35.5 p<0.001). During follow-up pacemaker was implanted in 35.5% of myectomy-group for atrioventricular block, 9.7% peri-operatively, and 25.8% during late follow-up. Furthermore, the pacing group had a superior freedom from all types of re-interventions, 90.3% versus 61.3% in myectomy-group (p=0.003). Pacing patients had a significant shorter in-hospital stay and costs compared to myectomy. **Conclusions**: 1) Heart failure was a dominant cause of death in this unselected geographical cohort of HOCM patients. Independent risk factors for disease, and specifically heart failure-related deaths, were female sex, age and persisting LVOT-obstruction. 2) Beta-blocker therapy aiming for doses of at least 150 mg/day metoprolol equivalents would be beneficial even in asymptomatic LVOT-obstruction. 3) Short atrioventricular delay pacing as a simple, cost-effective procedure with low rate of perioperative complications, and a low need for later re-interventions, was not inferior to myectomy in the relief of LVOTO and should thus be considered a valid option to treat patients with HOCM. 4) Early recognition in females, with a more liberal, and earlier, use of adequate treatment to optimize gradient-control and diastolic function, might improve the outcome in females with HOCM.

Key Words: Hypertrophic obstructive cardiomyopathy; myectomy; pacing; beta-blocker; survival; sex and re-intervention rate.

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