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Research Article

Reduced exercise tolerance is associated with a higher risk of malignant ventricular arrhythmias

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ABSTRACT

Malignant ventricular arrhythmia (MVA) is one of the most frequent causes of mortality among patients with cardiovascular disease. Exercise tolerance is a powerful variable to evaluate the cardiopulmonary system condition. The proposal of this research is to establish an association between peak oxygen uptake (VO_2) and the incidence of long-term malignant ventricular arrhythmia**.**

Methods: A historical cohort of patients with heart disease of a third level hospital of cardiology were studied. Every patient performed a symptoms-limited cardiopulmonary exercise testing and were followed-up to10 years. We defined malignant ventricular arrhythmia (MVA) as a combined outcome composed by tachycardia or ventricular fibrillation, implantation of a cardioverter (ICD) or sudden death. Patients were split in 2 groups according to MVA. Using a ROC curve, peak VO_2 was divided in two groups, according to a 25 mlO_2/kg/min cut-point. Bivariate analysis identified those variables associated with MVA, that were included in a multivariable regression Cox model. All p values less than 0.05 were considered stochastically significant.

Results: A total of 1767 individuals were studied, and 116 combined outcomes occurred. After Cox regression analysis, four variables were identified as statistically significant risk-factors for MVA: reduced VO_2 (HR 1.75, CI 95% 1.04 to 2.92), heart failure (HR 6.15, CI 95% 2.85 to 13.21), history of ICD (HR 2.12, CI 95% 1.26 to 3.55) and diuretic use (HR 2.6, CI 95% 1.6 to 4.2).

Conclusion: Maximal exercise tolerance is strongly associated with a long-term occurrence of malignant ventricular arrhythmia, together with other variables such as heart failure, history of previous ICD or diuretic use.

Introduction

Cardiovascular diseases are the most common cause of mortality in the world, especially associated to malignant ventricular arrhythmia [1]. Some attributable mechanisms are: abnormal function of the autonomic nervous system, re-entry or ischemia [2]. Physical exercise is a worldwide used manoeuvre to identify underlying heart pathology in susceptible individuals [3, 4]. Some authors have found a strong

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relationship between low exercise tolerance and survival. Therefore, we aimed to stablish an association between peak oxygen uptake (peak VO2) and the occurrence of malignant ventricular arrhythmia (MVA) [5-9].

Materials and Methods

A historical cohort of patients with heart disease that were referred to a third level cardiology hospital were studied. Baseline information was obtained of clinical records and every patient performed a symptom-limited cardiopulmonary exercise testing. ECG leads were placed according to the Mason-Likar method and ECG signal was recorded throughout the test. Blood pressure, symptoms and perceived exercise effort were measured at baseline, exercise and recovery. All individuals were pushed to their maximum effort, unless they presented an absolute indication to stop the test [10, 11]. A Schiller CS-200 © device was used. All patients underwent a three minutes period of active recovery. Then, they rested at supine position 5 more minutes. Medication was not suspended before exercise test. Both, standard stress test and cardiopulmonary variables were obtained.

Patients were followed up for 10 years (mean) and adverse outcome were recorded. We defined malignant ventricular arrhythmia (MVA) as a combined outcome, composed by tachycardia or ventricular fibrillation, implantation of a cardioverter (ICD) or sudden death. Those patients with previous ICD were considered to have the combined outcome only if they died or, if they had a life-threatening ventricular arrhythmia. Statistical analysis was performed using SPSS 21 software. Continuous variables are presented as mean (standard deviation) or median (range) as convenience. Bivariate analysis was performed using X2-square test or Student t-test for independent groups.

Patients were split in 2 groups according the presence or absence of MVA. Using a ROC curve, peak VO2 was divided in two groups, according to a 25 mlO2/kg/min cut-point. Those stochastically significant variables were recruited in a Cox proportional multivariable model, using a forward-Wald method. A Kaplan and Meier curve were displayed according to peak VO2. All p values less than 0.05 were considered stochastically significant.

Results

A total of 1767 patients were analysed. One hundred and sixteen subjects have had a combined outcome. Demographic characteristics and stress-testing variables are shown in (Tables 1 and 2). After multivariable analysis, only four variables remained significant: reduced VO2, heart failure, history of ICD and diuretic use.
Multivariable Cox regression model is shown in (Table 3) and Kaplan and Myer curve are displayed in (Figure 1).

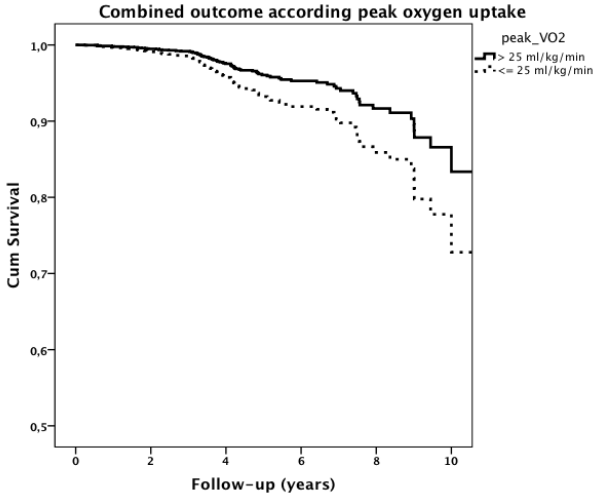

Figure 1

Discussion

Peak oxygen uptake has been widely proved as a predictive variable for all-cause mortality [12, 13]. Currently, there is a large number of evidence available showing cut-off points of peak VO2 in risk stratification of patients with heart failure, heart transplantation, among others [14-16]. However, the relationship between peak VO2 and malignant ventricular arrhythmia has not yet established. Our results show that low peak VO2 is associated with a long-term occurrence of MVA. These results are similar to findings of Correale et al (2013, 36-43), they found that patients with heart failure and episodes of sustained ventricular tachycardia had lower peak VO2 values [17].

The main importance of our study lies in the association between a low peak VO2 and malignant ventricular arrhythmia, that remains significant beyond a multivariable analysis. Assessment of peak VO2 may provide an additional prognostic factor in prediction of MVA. The presence of diuretic intake, previous ICD or heart failure should be taken in count at the time for predicting MVA in patients with heart disease. The mechanisms that could explain this association are partially explained. Patients with lower peak VO2, particularly those with reduced left ventricular ejection fraction have higher left ventricular filling pressure and ventricular stretch could trigger ventricular arrhythmias. Moreover, these patients show an augmented influence of activation of neurohormones and pro-inflammatory cytokines. Among these biomarkers, plasma values of norepinephrine, brain natriuretic peptide (BNP) and soluble tumour necrosis factor increase inversely to maximum exercise tolerance [18, 19]. An important limitation of this study is its retrospective approach.

Table 1: Demographic characteristics.

Patients	All (n= 1767)	MVA (n=116)	No-MVA (n=1651)	p value
Age (years)	51 ± 18	53 ± 13	50 ± 18	<0.05
Male gender (n %)	1387 (78%)	97(84)	1290 (78)	ns
BMI (kg/m^2)	26 ± 5	26 ± 4	26 ± 5	ns
CAD (n,%)	1281 (73)	80 (69)	1201 (73)	ns

VHD (n,%)	14 (1)	0 (0)	14 (1)	ns
CHD (n,%)	72 (4)	1 (1)	71 (4)	ns
Heart failure (n,%)	724 (41)	93 (80)	631 (38)	< 0.05
CABG (n,%)	69 (4)	10 (9)	59 (4)	< 0.05
PTCA (n,%)	676 (38)	21 (18)	655 (40)	< 0.05
ICD (n,%)	76 (4)	19 (16)	57 (4)	< 0.05
ACE-I (n,%)	1326 (75)	106 (91)	1220 (74)	< 0.05
Digoxin-use (n,%)	354 (20)	59(51)	295 (18)	< 0.05
Beta-blocker-use (n,%)	1349 (76)	96 (83)	1353 (76)	< 0.05
Anti-arrhythmic-use (n,%)	212 (12)	32 (28)	180 (11)	< 0.05
Diuretic-use (n,%)	553 (31)	77 (66)	476 (29)	< 0.05

Abbreviations. MVA (malignant ventricular arrhythmia), BMI (Body mass index), CAD (coronary heart disease), VHD (valvular heart disease), CHD (congenital heart disease), CABG (coronary artery bypass graft); PTCA percutaneous transluminal coronary angioplasty), ICD (history of cardio-defibrillator implantation), ACE-I (angiotensin-converting enzyme inhibitor).

Table 2: Cardiopulmonary exercise test.

Patients	All (n= 1767)	MVA (n=116)	No-MVA (n=1651)	p value
Resting HR (bpm)	70 ± 15	72 ± 14	70 ± 14	ns
Resting SBP (mmHg)	112 ± 17	106 ± 14	112 ± 16	< 0.05
Resting DBP (mmHg)	72 ± 11	70 ± 8	72 ± 11	< 0.05
Maximal HR (bpm)	137 ± 26	135 ± 24	137 ± 27	ns
Maximal SBP (mmHg)	144 ± 26	134±24	145±26	< 0.05
Maximal DBP (mmHg)	86 ± 18	82 ± 13	86 ± 18	< 0.05
Maximal achieved HR (%)	82 ± 14	81 ± 13	82 ± 13	ns
Exercise time (min)	9 ± 3	8 ± 3	9 ± 3	< 0.05
HR recovery (bpm)	18 ± 11	15 ± 12	18 ± 11	< 0.05
Arrhythmia (n,%)	876 (50)	93 (81)	783 (48)	< 0.05
Positive for Ischemia (n,%)	296 (17)	18 (16)	278 (17)	ns
Duke score	7 ± 6	6 ± 6	7 ± 6	ns
Maximal RQ	1.13 ± 0.12	1.14 ± 0.10	1.13 ± 0.12	ns
Peak VO_2 (mlO_2/kg/min)	23 ± 8	21 ± 7	23 ± 8	< 0.05
VE/VCO_2 slope	30 ± 6	31 ± 5	30 ± 6	ns
VO_2 recovery (s)	223 ± 150	234 ± 80	222 ± 153	ns

HR (heart rate), bpm (beats per minute), SBP (systolic blood pressure), DBP (diastolic blood pressure), HR recovery (first minute post-maximal exercise), FVE (frequent ventricular ectopy), Duke Score (treadmill Duke Score), RQ (respiratory quotient), VE/VCO_2 slope (ventilatory efficiency), VO_2 recovery (time for recovering to half value of peak VO_2)

Table 3: Multivariable Cox regression model.

Variable	B coefficient	Exp (B)	95% CI for Exp B		p value
Reduced peak VO_2	0.557	1.75	1.04	2.92	< 0.05
Diuretic use	0.954	2.60	1.60	4.21	< 0.01
Heart failure	1.816	6.15	2.85	13.21	< 0.01
ICD	0.749	2.12	1.26	3.55	< 0.01

Reduced peak VO_2 ($\leq$ 25 mlO_2/kg/min), ICD: implantable defibrillator.

Conclusion

Maximal Exercise tolerance is strongly related with long term occurrence of malignant ventricular arrhythmia, together with other variables such as diuretics, heart failure, or a previous ICD implant.

Authorship and contributorship

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