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Research Article

Exercise Contractile Reserve for Predicting Mortality in Non-Ischemic Ventricular Dysfunction

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A B S T R A C T

Objectives: A preserved contractile reserve is a marker of favorable outcome in different cardiac diseases. In some studies, using drugs, an increase in left ventricular (LV) systolic function was associated to better prognosis in patients with dilated cardiomyopathy. We aimed to assess whether a positive contractile reserve (CR) to physical exercise is a marker of good outcome in patients with LV systolic dysfunction not related to coronary artery disease (CAD).

Design: From our exercise echocardiography database we extracted patients with LV systolic dysfunction (LVEF ≤45), negative coronary angiography, and absence of a history of CAD. A positive CR was considered when peak LVEF was higher that resting LVEF. The endpoint was overall mortality.

Results and Conclusions: Among the 225 patients included, 105 had a positive CR and 120 a negative CR. Resting LV function was similar in patients with positive and negative CR (LVEF 35±8 vs. 34±9; wall motion score index 1.81±0.34 vs. 1.80±0.29; both p=NS). During a follow up of 6.2+4.7 years (25-75th percentiles 2.2-9.5), there were 71 deaths. Ten-year mortality rates were 34% for patients with CR and 67% for patients without CR (p=0.003). After multivariate adjustment that included clinical variables, medications, resting LV function, and exercise testing variables the only predictors of death were age (hazard ratio (HR) 1.07, 95% Confidence Interval (CI) 1.04-1.10, p<0.001), and absence of CR (HR 1.80, 95% CI 1.09-2.98, p=0.02). In conclusion, in patients with non- ischemic LV dysfunction, a positive CR to physical exercise is a marker of better outcome.

A preserved contractile reserve is a marker of favorable outcome in different cardiac diseases [1, 2]. In some studies, using pharmacological stress echocardiography, an increase in LV function with drugs has been associated to better prognosis in patients with dilated cardiomyopathy [1, 3-7]. We aimed to assess whether a positive contractile reserve (CR) to physical exercise is a marker of better outcome in patients with LV systolic dysfunction not related to coronary artery disease (CAD).

Methods

I Patients

This is a retrospective analysis of patients included in the CHUAC Stress Echocardiography Database with the following characteristics:

1. Left ventricular (LV) dysfunction as defined as a resting LV ejection fraction of ≤45
2. normal coronary arteries or non-significant (<50%) coronary stenoses in a coronary angiography
3. absence of a history of CAD

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4. absence of moderate or severe mitral or aortic valve disease, and
5. ability to exercise in a treadmill. Only the first ExE was considered. Patients were studied during a 20-year period from 1995 to 2015.

II Exercise echocardiography (ExE)

ExE was performed in a treadmill according to different protocols, adjusted to the clinical characteristics of the patients (Bruce protocol 88%, modified protocols 12%). Exercise end points included physical exhaustion, significant arrhythmia, severe hypertension (systolic BP >240 mm Hg or diastolic BP >110 mm Hg), severe hypotensive response (decrease >20 mm Hg), or symptoms during exercise. Ischemic ECG was defined as the development of ST-segment deviation of ≥1 mm which was horizontal or downsloping away from the isoelectric line 80 ms after the J point in at least 2 leads, in patients with normal baseline ST segments. The ECG was considered non-diagnostic in the presence of left bundle branch block, preexcitation, paced rhythm, repolarization abnormalities or treatment with digoxin. Positive exercise testing was defined as chest pain during the test and/or ischemic ECG abnormalities in patients with diagnostic ECG [8, 9]. A maximal test was defined as the achievement of at least 85% of the mean age-predicted heart rate (MAPHR), otherwise the test was considered submaximal.

Echocardiography was performed in 3 apical views (long axis, 4-, and 2-chambers) and 2 parasternal views (long- and short-axis) at baseline and at peak exercise [9, 10]. Regional wall motion abnormalities (WMA) were evaluated with a 16-segment model of the left ventricle [11]. Each segment was graded on a 4-point scale, with normal wall-motion scoring = 1, hypokinetic = 2, akinetic = 3, dyskinetic = 4. However, isolated hypokinesia of the basal inferior or infero-septal segments was not considered abnormal [12]. Wall motion score index (WMSI) and visually estimated left ventricular ejection fraction (LVEF) were calculated at rest and at peak exercise. In case of doubts regarding assessment of LVEF either at rest or at exercise or assignation of increase or decrease of LVEF with exercise, volumetric assessment by the Sympson biplane method was used [11, 13]. A positive contractile reserve was defined as an increase in LVEF from rest to exercise ≥ 1.

III Coronary angiography

Coronary angiographies were performed at a median of 89 days after the ExE study (25th-75th percentiles 7-294 days). For the purposes of this study, only patients with non-significant coronary stenoses (≤50% of narrowing by visual assessment) or normal coronary arteries were included.

IV Follow-up and endpoints

Follow-up was obtained by review of hospital databases, medical records, and death certificates, as well as by telephone interviews when necessary. The endopoint was overall mortality. No patients were lost during follow-up.

V Statistical analysis

Categorical variables were reported as % and continuous variables as mean ± 1 standard deviation. Event rates were calculated by dividing the number of events by the total number of person-years at risk. Survival free of the end point of interest was estimated by the Kaplan-Meier method, and survival curves were compared with the log-rank test. Univariable and multivariable associations of the different variables with outcome were assessed with Cox's proportional hazard model. Variables were selected in a stepwise forward selection manner, with entry and retention set at p=0.05. Hazard ratios (HR) with 95% confidence intervals (CI) were estimated.

The incremental value of ExE results, over clinical, resting echocardiographic and exercise treadmill testing variables was assessed in steps. The 1st step was based on clinical data. Resting echocardiographic data and exercise ECG data were then added in the following step. The final step consisted of ExE data (contractile reserve, peak exercise LVEF). Statistical analysis was performed using SPSS software, version 15.0 (SPSS, Chicago, IL).

Table 1: Clinical baseline characteristics, medications and coronary angiographic results.

	All patients	(+) CR	(-) CR	Value of p
Male gender, n (%)	160 (71)	76 (72)	84 (70)	0.69
Age (y)	64±10	63±10	65±10	0.07
Diabetes mellitus, n (%)	47 (21)	18 (17)	29 (24)	0.20
Hypertension, n (%)	125 (56)	52 (50)	73 (61)	0.09
Atrial fibrilation, n (%)	40 (18)	20 (19)	20 (17)	0.64
Left bundle branch block, n (%)	80 (36)	40 (38)	40 (33)	0.46
Abnormal resting ECG, n (%)	155 (69)	76 (72)	79 (66)	0.29
Reasons for testing, n (%)				
Non coronary chest pain	30 (13)	11 (10)	19 (16)	0.50
Atypical angina	94 (42)	41 (39)	53 (44)	
Typical angina	15 (7)	8 (8)	7 (6)	

Dyspnea Others	56 (25) 30 (13)	24 (23) 21 (20)	32 (27) 9 (8)	
Medications				
Betablockers*, n (%)	14 (6)	6 (6)	8 (7)	0.77
Calcium channel blockers, n (%)	21 (9)	4 (4)	17 (14)	**0.01**
Nitrites, n (%)	39 (17)	15 (14)	24 (20)	0.26
AECI/ARAs, n (%)	111 (49)	50 (48)	61 (51)	0.63
Digoxin, n (%)	23 (10)	15 (14)	8 (7)	0.06
Diuretics, n (%)	41 (18)	20 (18)	21 (18)	0.76
Angiography				
Normal coronary tree, n (%)	169 (75)	78 (75)	91 (76)	0.79
Nonsignificant coronary stenoses, n (%)	56 (25)	27 (25)	29 (24)	

*at the time of the ExE

Abbreviations: ACEI, angiotensin converting enzyme inhibitors; ARA, angiotensin receptor antagonists.

Table 2: Exercise echocardiography results.

	All patients	(+) CR	(-)CR	Value of p
Symptoms during ExE, n (%)	43 (19)	13 (12)	30 (25)	0.02
Exercise ECG testing, n (%)				
- negative	56 (25)	27 (26)	29 (24)	0.30
- positive	14 (6)	2 (2)	12 (10)	0.01
- non Dx	155 (69)	76 (72)	79 (66)	0.29
Maximal achieved workload (METs)	8.2±3.1	8.8±3.2	7.7±2.9	0.004
Heart rate (bpm)				
Rest	85±17	85±17	86±18	0.79
Exercise	152±25	152±26	152±24	1.00
% Achieved of the MAPHR	98±16	97±15	98±18	0.41
Blood pressure (mmHg)				
Rest	134±20	133±20	134±20	0.69
Exercise	161±31	162±30	161±31	0.68
Double product (mmHg x lpm x 10 [(3)])	11.4±2.7	11.3±2.9	11.4±2.6	0.74
Rest	24.7±6.4	24.9±6.4	24.5±6.5	0.67
Exercise				
LV ejection fraction (%)				
Rest	34±8	35±8	34±9	0.53
Exercise	35±10	40±10	31±8	<0.001
Δ in LVEF	1±6	5±4	-3±4	<0.001
Wall motion score index				
Rest	1.80±0.31	1.81±0.34	1.80±0.29	0.62
Exercise	1.82±0.34	1.70±0.38	1.92±0.26	<0.001

* <85% of the maximal age-predicted heart rate

Results

Table 1 shows the clinical characteristics of the patients and (Table 2) the ExE results. During a follow-up of 15±6 years, there were 71 deaths. (Table 3) shows the univariable and multivariable predictors of overall mortality, and (Figure 1) the survival curves for patients with and without contractile reserve during exercise. Five-year mortality rates were 12% for patients with contractile reserve and 20% for patients without contractile reserve, whereas ten-year mortality rates were 34% and 67%, respectively (p=0.003). Video 1 is an example of a patient with a positive contractile reserve to exercise.

Table 3: Predictors of overall mortality.

	Univariable			Multivariable		
	HR	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Clinical variables						
Age (per year)	1.07	1.04-1.10	<0.001	1.07	1.04-1.10	<0.001
Resting double product HR x BP	0.91	0.82-1.00	0.04			
Digoxin	0.38	0.16-0.91	0.03			
Exercise testing						
METs	0.87	0.80-0.95	0.002			
Peak double product HR x BP	0.96	0.93-1.00	0.04			
ExE						
Δ LVEF	0.96	0.93-1.00	0.048			
No contractile reserve	2.07	1.26-3.40	0.004	1.80	1.09-2.98	0.02

METs denotes metabolic equivalents; LVEF, left ventricular ejection fraction; HR, heart rate; BP, blood pressure.

*Other non-significant analyzed variables were hypertension, hypercholesterolemia, smoking, treatment with nitrites, treatment with calcium channel blockers, treatment with angiotensin converting enzyme inhibitors or angiotensin receptor antagonists, treatment with diuretics, atrial fibrillation at the time of the ExE, left bundle branch block, abnormal resting ECG, Δ in double product from rest to exercise, symptoms during exercise testing, positive exercise testing, resting and exercise LVEF, resting and exercise WMSI, and Δ in WMSI.

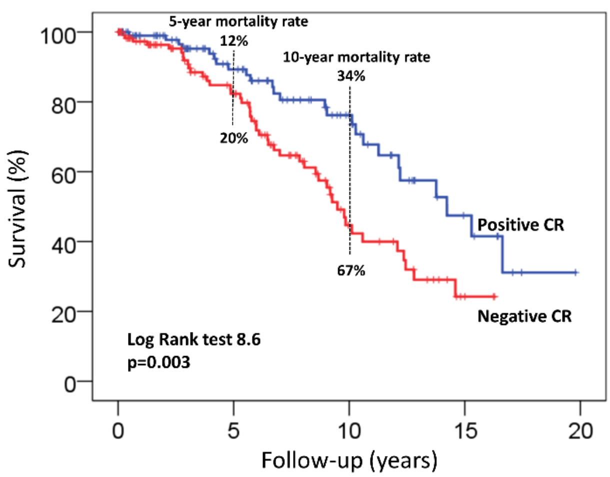

Figure 1: Kaplan-Meier survival curves for patients grouped according to the presence or absence of contractile reserve to exercise.

Discussion

To our knowledge this is the first study that has demonstrated the clinical value of ExE for assessment of contractile reserve in patients with non-ischemic LV dysfunction. ExE allowed better stratification of outcome, as overall mortality was almost double in patients without contractile reserve, in comparison with those with contractile reserve. In fact, mortality rate differed early after the ExE stratification. Old studies have already assessed the usefulness of measurement of contractile reserve with exercise in combination with imaging by radionuclides to define outcome in patients with dilated cardiomyopathy [14]. Later on, there has been a myriad of investigations using dobutamine or dypiridamol for assessment of contractile reserve in patients with LV dysfunction of either non-ischemic or ischemic origin, also showing similar findings, in terms of more favorable outcome for those with a positive response [1, 3-7]. A recent metaanalysis including mostly pharmacological stress echocardioghraphy studies also showed better outcome in patients with LV dysfunction and contractile reserves, with a 20% lower probability of events in those with a positive contractile reserve [15]. However, dobutamine stress echocardiography may be more harmful that exercise echocardiography, particularly in patients with LV dysfunction [16-17]. Also, the kind of response to stress with dobutamine or with exercise has been employed in an attempt to discriminate whether a LV dysfunction was due to an ischemic or non-ischemic disease in previous research [18, 19]. As expected, ischemic responses like a biphasic response to dobutamine, or worsening with exercise or dobutamine, are found more frequently when LV dysfunction is associated to CAD, and these responses confer bad outcome [19, 20]. However, as demonstrated in the current study, patients with LV dysfunction not associated to CAD may still have worsening of LV function with exercise, and this LV performance portended a worse outcome. Finally, in the last years some investigators have used exercise echocardiography to predict LV heart response to remodeling after cardiac resynchronization therapy in patients with ischemic or non-ischemic LV dysfunction and left bundle branch block, with promising results. The presence of contractile reserve during exercise was associated to a greater chance of response to resynchronization therapy in these studies [21, 22].

CAD was reasonably excluded for most of our patients, as coronary angiography was entirely normal or showed only non-significant lesions. Explanations for lack of contractile reserve in half of our patients might include higher amount of fibrosis that could involve myocardium and/or microvasculature, as well as relative increase in afterload of an already dysfunctional ventricle. A lack of contractile reserve might lead to development or worsening of mitral regurgitation, cardiac failure, and arrhythmias [23]. A contractile reserve to exercise has been found to be associated to other markers of poor outcome like maximum O2 consumption and functional capacity [24]. Our patients with a negative CR also had worse functional capacity that those with a positive CR.

Limitations

The main limitation is the extended period of follow-up with changing criteria and cut-offs for referring patients to angiography and devices implantation. Thus, patients without contractile reserve might have gone to coronary angiography with higher likelihood that those with contractile reserve, particularly at the beginning of the inclusion period. The impact on outcome of defibrillators and resynchronization therapy were also not measured.

Also, concerns may arise on the visual assessment for the majority of the patients of LVEF at rest and exercise and the assignments of positive or negative CR. Nevertheless, in a previous study of our group in patients with LV systolic dysfunction the concordances for assignments of increase/decrease LVEF with exercise was moderate (83% intra-observer and 87% inter-observer with kappa values of 0.67 and 0.73, respectively) [19].

Conflicts of interest

There is not conflict of interest.

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