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Dobutamine-Induced Mechanical Alternans

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1. Introduction

We investigated the relationship between the occurrence of dobutamine-induced mechanical alternans (MA) and prognosis in ambulatory patients with idiopathic dilated cardiomyopathy (IDCM).

Recent American College of Cardiology and American Heart Association guidelines for the management of heart failure have emphasized the need for earlier identification and therapy for patients at high risk of systolic dysfunction, as well as for those with symptomatic heart failure.

MA, a condition characterized by beat-to-beat oscillation in the strength of cardiac muscle contraction at a constant heart rate, has been observed in patients with severe heart failure and in animal models of this condition.

Although MA is rare under resting conditions in individuals with controlled heart failure, at higher heart rates it is more prevalent and likely to be sustained, as exemplified by pacing-induced MA or dobutamine-induced MA. However, few studies have addressed the clinical implications of dobutamine-induced MA in patients with heart failure. We therefore prospectively examined the prognostic value of dobutamine- and pacing- induced MA in ambulatory patients with IDCM in sinus rhythm.(1)

2. Methods

2.1 Patient population

We studied 90 patients with IDCM (mean age, 50 years; range, 20 to 76 years) and an New York Heart Association (NYHA) functional class of I or II. Thirty-eight of the patients had previously been admitted to hospital because of heart failure with dyspnea on exertion, palpitations, or peripheral edema, whereas the remaining 52 were asymptomatic and were identified on the basis of electrocardiogram abnormalities detected at annual health checkups. All patients had normal sinus rhythms. IDCM was defined by the presence of both a reduced left ventricular (LV) ejection fraction (<50%, as determined by contrast left ventriculography) and a dilated LV cavity.

2.2 Cardiac catheterization

All patients initially underwent routine diagnostic left and right heart catheterization. A 6F fluid-filled pigtail catheter with a high-fidelity micromanometer was advanced into the left ventricle through the right radial artery to measure LV pressure. Right atrial pacing was

initiated at 80 beats per minute (bpm) and was increased in increments of 10 bpm. We selected steady-state LV pressure data for at least 2 min at the baseline and at each pacing rate for analysis.(2) We calculated the maximum first derivative of LV pressure (LV dP/dt_{max}) as an index of contractility. To evaluate LV isovolumic relaxation, we computed the pressure half-time ($T_{1/2}$) directly, as previously described.(3) The peak pacing rate was defined as the heart rate at which second-degree atrioventricular block occurred. After the hemodynamic values had returned to baseline, dobutamine was infused intravenously at incremental doses of 5, 10, and 15 μg kg^{-1} b.w. min^{-1} and hemodynamic measurements were performed at the end of each 5-min infusion period. MA was diagnosed if the pressure difference between the strong and weak beats was ≥4 mm Hg continuously in the analyzed LV pressure data, as previously described.(4)

2.3 Quantitative RT-PCR analysis

Quantitative reverse transcription (RT) and polymerase chain reaction (PCR) analysis of the mRNAs for sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2a), ryanodine receptor 2, phospholamban, calsequestrin, and the Na^{+}-Ca^{2+} exchanger was performed as previously described.(5) The amount of each mRNA was normalized against the corresponding amount of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNA.

2.4 Follow-up

We prospectively followed up all patients for the occurrence of primary events, which were defined as cardiac death (death from worsening heart failure or sudden death), unscheduled hospital readmission for worsening heart failure, or receipt of an implantable cardioverter defibrillator (ICD) because of life-threatening arrhythmia.

3.Results

3.1 Classification of IDCM patients on the basis of MA

To identify on the basis of the classification by hemodynamic response to pacing or dobutamine stress testing, patients were classified into three groups: those who exhibited neither pacing- nor dobutamine-induced MA (n = 60, group N), those who manifested only pacing-induced MA (n = 20, group P), and those who developed both pacing- and dobutamine-induced MA (n = 10, group D). All patients who did not develop pacing-induced MA also did not exhibit dobutamine-induced MA. LV pressure waveforms during atrial pacing at 120 bpm or after dobutamine infusion at 10 μg kg^{-1} min^{-1} are shown for representative patients from each group (Fig. 1).

3.2 Baseline clinical data

There were no significant differences in age and sex among the three groups of patients (Table 1). All patients were classified as NYHA functional class I or II at the time of cardiac catheterization. The LV ejection fraction (LVEF) in groups P and D was significantly lower than that in group N. There were also no significant differences in plasma brain natriuretic peptide (BNP) or norepinephrine levels among the three groups.

3.3 Abundance of Ca^{2+}-handling protein mRNAs in endomyocardial biopsy specimens

The amounts of Ca^{2+}-handling protein mRNAs in endomyocardial biopsy specimens were determined by using quantitative RT-PCR and were normalized against that of GAPDH

mRNA (Table 2). The abundance of phospholamban mRNA was significantly lower in group D than in group P. The SERCA2a/phospholamban mRNA ratio was significantly higher in group D than in groups N and P.

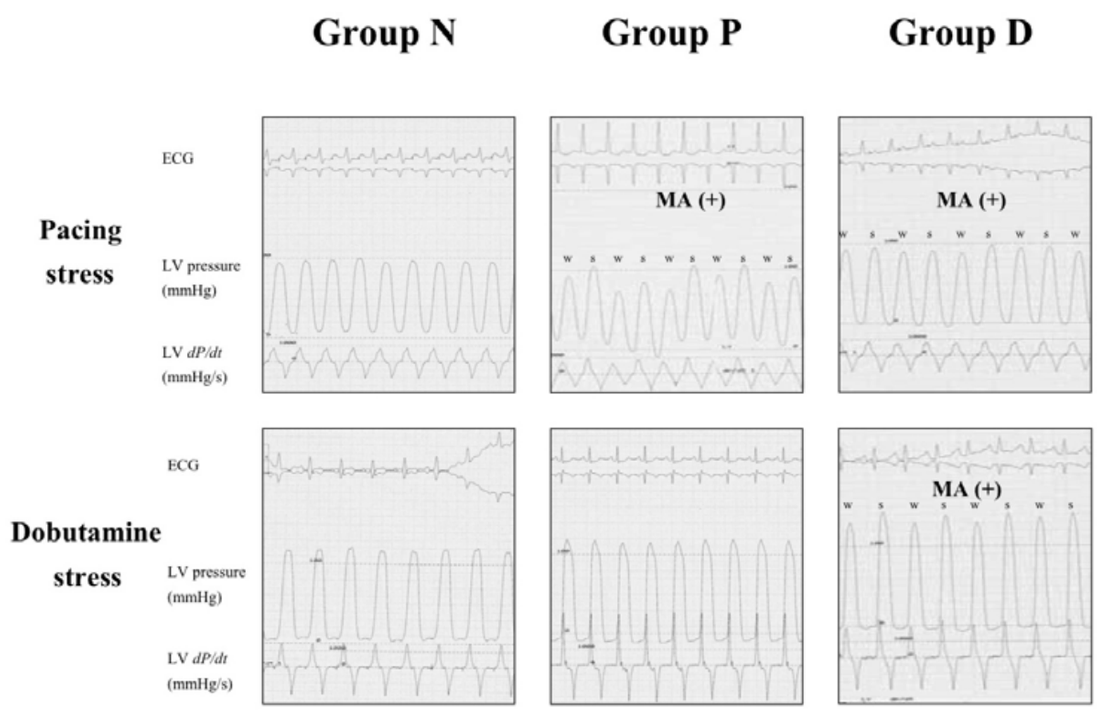

Fig. 1. LV pressure waveforms during atrial pacing at 120 bpm and after infusion of dobutamine at a dose of 10 μg kg^{-1} min^{-1} in representative patients of three study groups. The traces represent the lead II electrocardiogram (ECG), LV pressure, and LV dP/dt. Both LV dP/dt_{max} and LV dP/dt_{min} showed alternating changes with LV pressure. Strong and weak beats are indicated by s and w, respectively.

Characteristic	Group N (n = 60)	Group P (n = 20)	Group D (n = 10)
Age (years)	51 ± 12	50 ± 13	45 ± 11
Sex (M/F)	44 / 16	16 / 4	6 / 4
NYHA functional class I	32 (53%)	9 (45%)	5 (50%)
class II	28 (47%)	11 (55%)	5 (50%)
Medication			
Diuretics	30 (50%)	17* (85%)	9* (90%)
ACE inhibitors or ARBs	42 (70%)	19 (95%)	7 (70%)
Beta blockers	22 (37%)	10 (50%)	5 (50%)
PAWP (mmHg)	10.7 ± 4.7	14.6 ± 6.2*	13.9 ± 7.2
Cardiac index (L min^{-1} m^{-2})	3.07 ± 0.55	2.83 ± 0.58	3.26 ± 0.66
LVEF (%)	38.9 ± 8.1	32.9 ± 9.6*	30.3 ± 9.0*
Plasma BNP (pg/mL)	100 ± 173	179 ± 186	249 ± 262
Plasma norepinephrine (pg/mL)	440 ± 221	689 ± 764	664 ± 324

*P < 0.05 versus group N. Abbreviations not defined in text: ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; PAWP, pulmonary artery wedge pressure.

Table 1. Baseline clinical characteristics of patients in the three study groups

mRNA ratio	Group N	Group P	Group D
SERCA2a/GAPDH	0.42 ± 0.15	0.41 ± 0.13	0.43 ± 0.13
Phospholamban/GAPDH	0.82 ± 0.45	1.01 ± 0.13	0.42 ± 0.24*
Ryanodine receptor 2/GAPDH	0.50 ± 0.19	0.53 ± 0.21	0.75 ± 0.17
SERCA2a/phospholamban	0.63 ± 0.31	0.59 ± 0.40	1.32 ± 0.95*†
SERCA2a/Na^+-Ca^{2+} exchanger	0.57 ± 0.79	0.50 ± 0.56	0.27 ± 0.14

*P < 0.05 versus group P, †P < 0.05 versus group N.

Table 2. Quantitative RT-PCR analysis of the abundance of Ca^{2+}-handling protein mRNAs in endomyocardial biopsy specimens.

3.4 Follow-up evaluation and event-free survival

Of the 90 patients who were followed up, 4 individuals (4%) experienced cardiac death, 10 (11%) manifested worsening heart failure, and 4 (4%) received ICDs. The probability of event-free survival in group D was significantly lower than that in groups N or P (P = 0.002) (Fig. 2).

3.5 Univariate and multivariate analysis of cardiac events

Univariate analysis revealed that dobutamine-induced MA, pacing-induced MA, NYHA functional class, plasma BNP levels, mitral regurgitation, pulmonary artery wedge pressure, LV end-diastolic volume index, LV end-systolic volume index, LVEF, LV end-diastolic pressure and T½ were significant predictors of cardiac events (Table 3). Then, stepwise multivariate analysis identified dobutamine-induced MA (odds ratio, 4.05; 95% confidence interval, 1.35 to 12.2) as a significant independent predictor of cardiac events (Table 4). Both $T_{1/2}$ (odds ratio, 1.079; 95% confidence interval, 1.003 to 1.161) and plasma BNP level (odds ratio, 1.002; 95% confidence interval, 1.0004 to 1.0038) were also significant independent predictors of cardiac events, but with smaller odds ratios than that of dobutamine-induced MA.

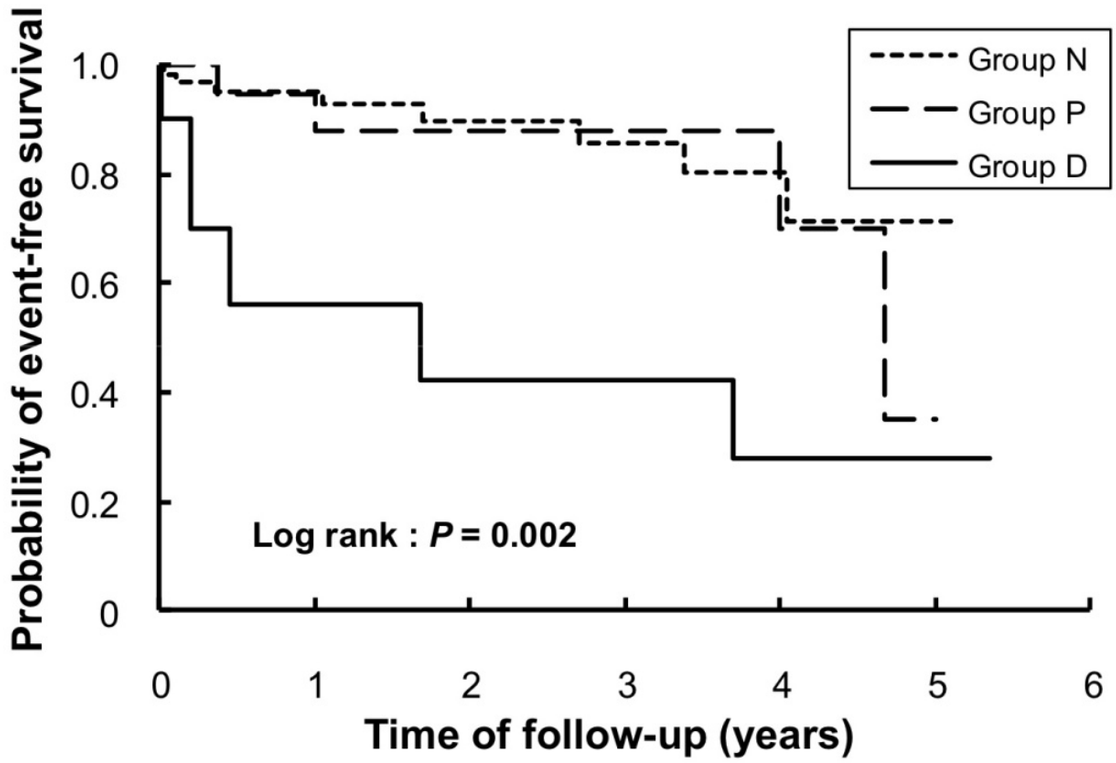

Fig. 2. Kaplan-Meier analysis of the cumulative probability of event-free survival of the 90 IDCM study patients. The probability of event-free survival in group D was significantly lower than that in groups P and N by the log-rank test (P = 0.002).

Parameter	Univariate analysis						
	Event-free group (n = 72)			Cardiac-event group (n = 18)			P
Dobutamine-induced MA (group D/groups P and N)	4	/	68	6	/	12	0.0019
Pacing-induced MA (groups D and P/group N)	20	/	52	10	/	8	0.04
Age (years)	50	±	12	53	±	14	0.34
Sex (M/F)	53	/	19	13	/	5	0.86
Body mass index (kg/m^2)	24.4	±	4.9	22.5	±	2.6	0.15
NYHA functional class	1.3	±	0.5	1.6	±	0.4	0.011
QRS duration (ms)	113	±	27	112	±	22	0.88
Beta blockers	55 (76%)			10 (56%)			0.58
Diuretics	52 (72%)			16 (89%)			0.88
Plasma BNP (pg/mL)	123	±	238	228	±	162	0.0013
eGFR (mL min^{-1} 1.73 m^{-2})	74	±	17	68	±	18	0.089
Plasma norepinephrine (pg/mL)	521	±	452	524	±	292	0.32
Mitral regurgitation	0.56	±	0.64	0.94	±	0.94	0.022
E/E'	15.6	±	8.6	24.2	±	8.4	0.227
PAWP (mmHg)	11.5	±	5.3	13.7	±	6.6	0.044
Cardiac index (L min^{-1} m^{-2})	3.02	±	0.57	3.13	±	0.64	0.85
LVEDVI (mL m^{-2})	73	±	52	115	±	79	0.02
LVESVI (mL m^{-2})	43	±	36	84	±	62	0.018
LVEF (%)	38.2	±	8.7	32.8	±	6.8	0.003
Heart rate (bpm)	76	±	17	75	±	14	0.34
LVEDP (mmHg)	12	±	8	15	±	9	0.019
LVSP (mmHg)	119	±	19	116	±	23	0.62
LV dP/dt_{max} (mmHg/s)	1114	±	263	1160	±	263	0.73
$T_{1/2}$ (ms)	39	±	7	44	±	4.7	0.0086

Table 3. Univariate of predictors of cardiac events.

Parameter	Multivariate analysis			
	β	OR	(95% CI)	*P*
Dobutamine-induced MA (group D/groups P and N)	1.4	4.05	(1.35–12.2)	0.0126
Plasma BNP (pg/mL)	0.0021	1.002	(1.0004–1.0038)	0.014
$T_{1/2}$ (ms)	0.076	1.079	(1.0033–1.161)	0.041

Table 4. Multivariate analysis of predictors of cardiac events.

4. Discussion

We found that the occurrence of dobutamine-induced MA was a clinical predictor of poor prognosis in ambulatory patients with IDCM in sinus rhythm. Although there was no significant difference in LVEF between patients who manifested only pacing-induced MA and those who developed both pacing- and dobutamine-induced MA, the probability of event-free survival in the latter group was significantly lower than that in the former. Multivariate analysis also revealed that the occurrence of dobutamine-induced MA was a significant independent predictor of cardiac events.

Our study included a group of 90 ambulatory patients with IDCM (mean LVEF of 36.5% and plasma BNP concentration of 132 pg/mL). We sought to investigate whether the hemodynamic response to dobutamine stress testing was associated with prognosis in such patients and could thereby serve as a physiological phenomenon on which risk stratification could be based. Three general mechanisms have been proposed to account for the development of MA: alteration of action potential duration, impaired ventricular relaxation, and abnormal intracellular Ca^{2+} handling.(6) The low relative ratio of phospholamban to SERCA reduces the inhibition of SERCA and increases Ca^{2+} -uptake; this enhances relaxation and contraction in the human atrium. However, humans lacking phospholamban develop lethal IDCM.(7) SERCA2a and ryanodine receptor 2 mRNA levels were similar in all three of our groups, whereas the relative ratio of SERCA to phospholamban was significantly higher in patients with pacing- and dobutamine-induced MA than in those with only pacing-induced MA or with no MA. Our results suggest that an imbalance between phospholamban and SERCA mRNA levels in the abundant Ca^{2+}-handling proteins is associated with dobutamine-induced MA. We also recently found that the amounts of mRNAs for the β_1-adrenergic receptor and SERCA2a in the myocardium were smaller in asymptomatic or mildly symptomatic IDCM patients with reduced adrenergic myocardial contractile reserve than in those with preserved adrenergic contractile reserves.(8) The occurrence of dobutamine-induced MA in our patients in the present study might also reflect abnormal β_1-adrenergic receptor signaling in the myocardium. However, steady-state mRNA levels do not necessarily reflect the

corresponding protein levels, in particular because both mRNA and protein synthesis or degradation may be altered in the failing heart.(9, 10) Further studies are needed to elucidate these issues.

In patients with heart failure, dobutamine-induced MA is highly prevalent(4) and mechanical and visible T-wave alternans is detectable under tachycardia or catecholamine exposure.(2, 11) Dobutamine-induced MA may be attributed various factors, including an increase in the heart rate as a result of dobutamine infusion, impaired LV contraction, the influence of preload, and abnormal Ca^{2+} under pathophysiological conditions. Dobutamine is a β-stimulator that increases both heart rate (HR) and LV contraction. The increase in HR, but not that in LV contraction, is likely to be a trigger for the occurrence of dobutamine-induced MA. Therefore, the increased occurrence of dopamine-induced MA in heart failure patients might be related to their poor myocardial contractile reserve

We reported previously that the occurrence of pacing-induced MA is a potentially useful indicator of poor prognosis in patients with mild-to-moderate IDCM in sinus rhythm.(2) Here, we found that, among our ambulatory IDCM patients, those with both pacing- and dobutamine-induced MA had the least favorable clinical course, whereas those with only pacing-induced MA had a moderate clinical course, even though the mean value of baseline LVEF did not differ significantly between these two groups.

Our results show that the occurrence of dobutamine-induced MA is a potentially useful clinical predictor of cardiac events in ambulatory patients with IDCM in sinus rhythm. Recent guidelines for the management of heart failure emphasize the need for earlier identification of and therapy for patients who are at high risk of developing heart failure or who have asymptomatic LV systolic dysfunction.(12) We showed here that the prevalence of cardiac events or cardiac death was higher in patients with dobutamine- and pacing-induced MA than in those without it. Assessment of dobutamine-induced MA in addition to routine clinical evaluation in patients with IDCM may thus contribute to stratification of individuals into low- or high-risk groups.

Our study had several limitations. First, it included only a small number of patients. Second, the identification of pacing- or dobutamine-induced MA requires an invasive examination and time-consuming hemodynamic stress assessment. The current trend in clinical medicine is to find a non-invasive test with prognostic consequences. However, these results of the present study suggested that the hemodynamic phenomenon by dobutamine stress testing might be also potentially useful marker for predicting the occurrence of cardiac events. The fact that such examinations are not amenable to being repeated over time is a potential limitation of their prognostic utility. Whether our findings will also hold for patients with more severe heart failure requires further investigation.

In conclusion, the occurrence of dobutamine-induced MA is a potentially useful clinical predictor of poor prognosis in ambulatory patients with IDCM in sinus rhythm.

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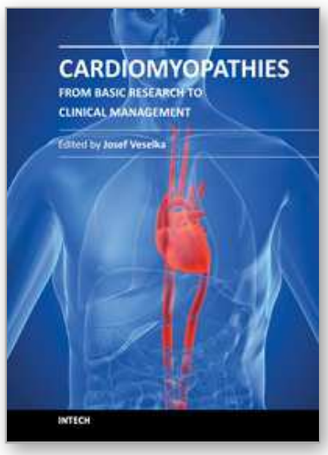

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Cardiomyopathy means "heart (cardio) muscle (myo) disease (pathy)". Currently, cardiomyopathies are defined as myocardial disorders in which the heart muscle is structurally and/or functionally abnormal in the absence of a coronary artery disease, hypertension, valvular heart disease or congenital heart disease sufficient to cause the observed myocardial abnormalities. This book provides a comprehensive, state-of-the-art review of the current knowledge of cardiomyopathies. Instead of following the classic interdisciplinary division, the entire cardiovascular system is presented as a functional unity, and the contributors explore pathophysiological mechanisms from different perspectives, including genetics, molecular biology, electrophysiology, invasive and non-invasive cardiology, imaging methods and surgery. In order to provide a balanced medical view, this book was edited by a clinical cardiologist.

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