Chapter 6

Dobutamine-Induced Mechanical Alternans

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1. Introduction

Mechanical alternans (MA) is a mysterious phenomenon. 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 and compared the prognostic value of dobutamine- and pacing- induced MA in ambulatory patients with idiopathic dilated myocardiopathy (IDCM) in sinus rhythm.[1] Furthermore, this review addresses the clinical circumstances, relevance of MA, current understanding with ideas about its mechanism, and some future perspectives.

2. Mechanical Alternans (MA)

2.1. History of MA

Phenomenon of alternating weak and strong beats observed in a heart which is contracting with constant intervals between beats. It has a long history. Experimental descriptions first appeared over a century ago, and since then there has been a sustained debate among clinicians and physiologists about its origins and clinical significance. A clinical description of an alternating pulse by Traube is often quoted as appearing earlier. [2] However, careful inspection of his figure shows alternating interbeat intervals. In fact, Traube himself commented on the alternation of intervals and used the term "bigeminus" in the title of his report, although the true nature of this arrhythmia can only be guessed at since the electrocardiograms had yet

to be invented at the time when Traube reported his case. MA has been studied in the intact human and animal heart, in isolated muscle preparations, and most recently in isolated cardiac muscle cells.

2.2. Induction of MA

The ability to induce MA by rapid driving frequencies appears to be a fundamental property of mammalian ventricular muscle. Experimental studies have shown that by varying the pacing cycle length over a wide range, it is possible to define a critical cycle length (threshold) for the induction of sustained MA.[3] Driving the heart at cycle lengths shorter than the threshold cycle length may increase the amplitude of the beat-to-beat oscillations in contraction strength.

3. Method

3.1. Pacing- and dobutamine- induced MA

It is more prevalent and likely to be sustained, as exemplified by pacing-induced MA. 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.[4] 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 $T_{1/2}$, as previously described.[5] After the hemodynamic values had checked at baseline, dobutamine was infused intravenously at incremental doses of 5, 10, and 15 μg $kg^{-1}min^{-1}$ 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 mmHg continuously in the analyzed LV pressure data, as previously described.[6]

We prospectively followed up all patients for the occurrence of primary events, which were defined as cardiac death (from worsening heart failure or sudden death) or the unscheduled readmission for decompensated heart failure. Noncardiac death was excluded.

4. Results

4.1. Classification of IDCM patients on the basis of dobutamine-induced 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

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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).

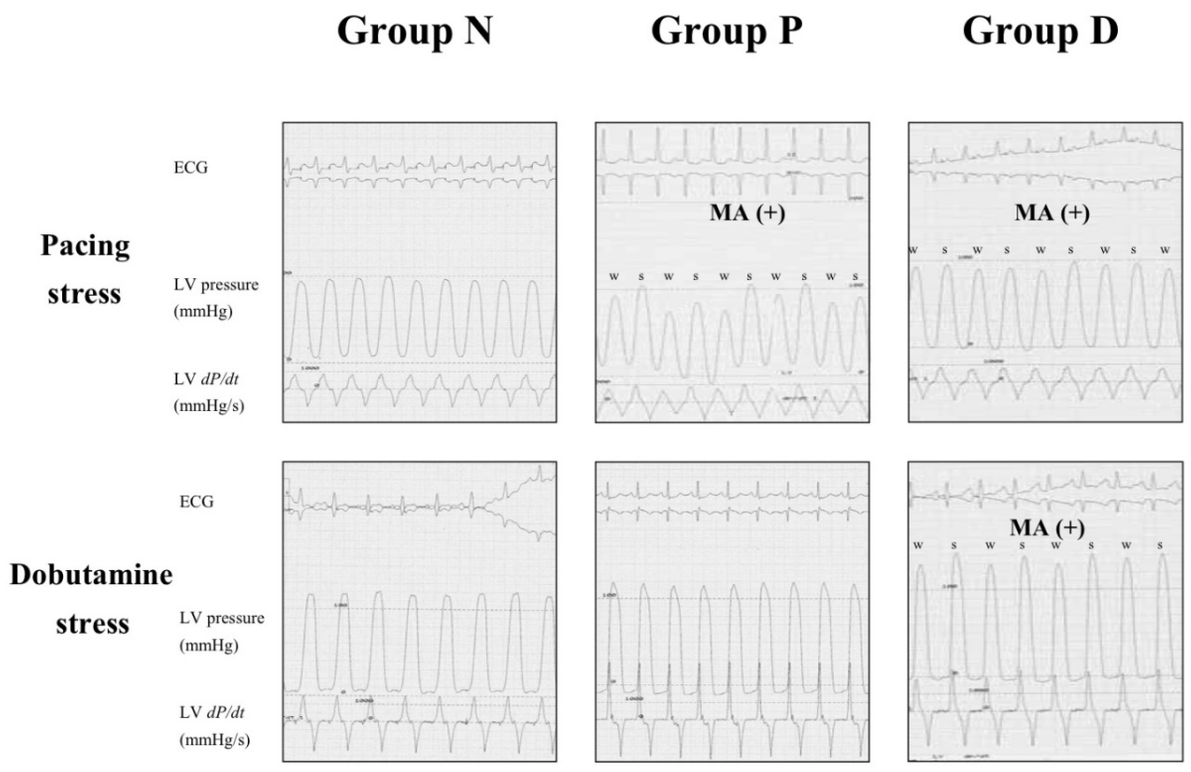

Figure 1. LV pressure waveforms during atrial pacing at 120 bpm and after infusion of dobutamine at a dose of 10 μg kg^{-1} min^{-1} in representative patients of three study groups. The traces represent the lead II electrocardiogram (ECG), LV pressure, and LV dP/dt. Both LV dP/dt_{max} and LV dP/dt_{min}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

4.2. 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 (EF) 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.

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 (Table 2). The probability of event-free survival in group D was significantly lower than that in groups N or P (P = 0.002) (Fig. 2).

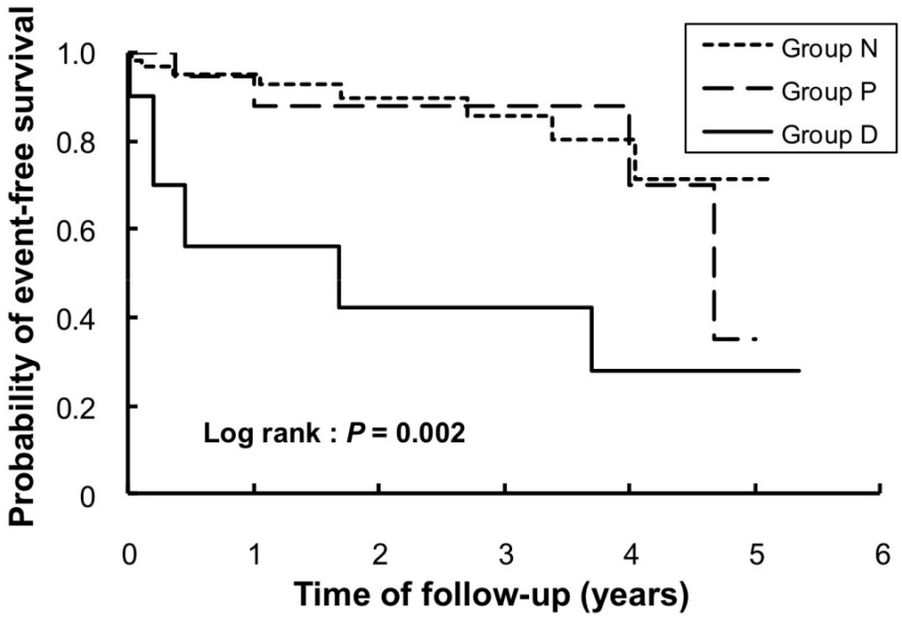

Figure 2. Kaplan-Meier analysis of the cumulative probability of event-free survival of the 90 IDCM study patients. Cardiac events were defined as hospitalization due to worsening heart failure and cardiac death. The probability of event-free survival in group D was significantly lower than that in groups P and N by the log-rank test ($P = 0.002$).

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.

4.3. 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 $T_{½}$ 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.

	Univariate analysis						
Parameter	Event-free group			Cardiac-event group			*P*
	(n = 72)			(n = 18)			
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

Parameter	Univariate analysis						P
	Event-free group (n = 72)			Cardiac-event group (n = 18)			
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
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)	0.013
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.

5. Impact of dobutamine-induced MA

5.1. Prognosis

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 dif-

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ference 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.

5.2. Mechanisms

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.[7] 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.[8] 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. These results suggest that an imbalance between phospholamban and SERCA mRNA levels in the abundant Ca^{2+}-handling proteins is associated with dobutamine-induced MA. Kobayashi et al. reported 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.[9] 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.[10, 11] Further studies are needed to elucidate these issues.

In patients with heart failure, dobutamine-induced MA is highly prevalent[6] and mechanical and visible T-wave alternans is detectable under tachycardia or catecholamine exposure.[4, 12] 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 and LV contraction. The increase in heart rate, 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.

6. Conclusion

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. 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 asymp-

tomatic LV systolic dysfunction.[13] 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. 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, the hemodynamic phenomenon by dobutamine stress testing might be also potentially useful marker for predicting the occurrence of cardiac events.

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