Mechanical Alternans in Patients With Chronic Heart Failure

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ABSTRACT

Background: Clinical implications of mechanical alternans in patients with chronic heart failure have remained uncertain. In this study, prevalence, characteristics, and prognostic implications of mechanical alternans were investigated.

Methods and Results: Consecutive 51 patients with dilated cardiomyopathy underwent diagnostic cardiac catheterization using a micromanometer-tipped catheter. Under basal conditions, 7 of 35 patients with sinus rhythm showed mechanical alternans. Physiologic tachycardia (110 bpm) induced mechanical alternans in another 15 patients with sinus rhythm and in another 10 of 16 patients with atrial fibrillation. Low doses of dobutamine also induced mechanical alternans in another 8 patients, but a high dose of dobutamine eliminated mechanical alternans. Consequently, 40 patients (78%) showed mechanical alternans. Mechanical alternans was always accompanied by alternating changes of positive dP/dt, a parameter of contractility during isovolumetric contraction time, but negative dP/dt was occasionally constant. Concordant mechanical alternans between both ventricles was more prevalent than discordant alternans. The left ventricular end-diastolic volume indices and end-systolic volume indices of patients with mechanical alternans were larger than those of patients without. The left ventricular ejection fraction of patients with alternans was significantly lower than that of patients without.

Conclusions: Mechanical alternans was highly prevalent in patients with chronic heart failure. The origin of mechanical alternans seems to exist before or at the isovolumetric contraction time.

Key words: mechanical alternans, chronic heart failure, dilated cardiomyopathy, dP/dt, sarcoplasmic reticulum.
Mechanical alternans is a mysterious phenomenon of alternating strong and weak beats with a constant beat to beat interval. The phenomenon has, for over a century, been recognized in patients with severe congestive heart failure caused by global left ventricular dysfunction (1–3). Other conditions related to the appearance of mechanical alternans are aortic stenosis (4), hypertrophic obstructive cardiomyopathy (5), sudden increase of afterload (6,7), ischemia (8,9), abrupt fall of preload, and the onset of a tachyarrhythmia (10–12). Experimental studies showed that mechanical alternans can be provoked in either whole hearts, isolated muscle preparations, and cultured isolated cardiomyocytes (13–15). Experimental preparations also showed that predisposing factors to mechanical alternans are extremely rapid heart rates, ischemia, negative inotropic interventions, cooling of the muscle, reduction of the extracellular Ca\(^{2+}\) concentration, and acidosis. In spite of the great interests by both physiologists and cardiologists, the precise mechanisms of human mechanical alternans and clinical implications of mechanical alternans still remain unclear.

Cardiac alternans can be classified into mechanical alternans and electrical alternans. Electrical alternans is composed of QRS alternans and ST-T alternans. QRS electrical alternans has been considered to be related to incomplete activation of the heart or changes of the ventricular activation process (16). Another possible relating condition for QRS alternans is positional oscillation of the heart in massive pericardial effusion. ST-T electrical alternans depends on the oscillation of the action potential duration. This form of electrical alternans leads to the dispersion of refractory periods of the myocardium. ST-T electrical alternans has been shown to be able to predict the occurrence of polymorphic ventricular tachycardia, ventricular fibrillation, and sudden cardiac death (17–20). Despite the clinical usefulness of electrical alternans, prognostic implications of mechanical alternans in patients with chronic heart failure are still unknown (21–23). The relevance among these subtypes of cardiac alternans is also uncertain.

In this study, we examined the frequency and features of mechanical alternans in patients with chronic heart failure. We also analyzed the relationship between the prevalence of mechanical alternans and left ventricular function. Mechanisms and prognostic implications of mechanical alternans in patients with chronic heart failure were also discussed.

**Methods**

**Patients**

Fifty-one consecutive patients with mild-to-severe left ventricular dysfunction, admitted to our hospital from November 1989 to May 1995 because of chronic or congestive heart failure, were included in the study (Table 1). Underlying heart diseases consisted of idiopathic dilated cardiomyopathy and postmyocarditic dilated cardiomyopathy. Patients with active myocarditis, significant valvular diseases, hypertensive heart diseases, hypertrophic cardiomyopathy, or ischemic heart diseases were excluded. Thirty-eight patients were men. Ages of the patients ranged from 21 to 71. Thirty-five patients had sinus rhythm, and the remainder had atrial fibrillation. The left ventricular end-diastolic volume indices ranged from 63 to 276 mL/m\(^2\). The left ventricular ejection fraction ranged from 13% to 59%. After admission to the hospital, congestive heart failure was controlled using diuretics, digitalis, and angiotensin-converting enzyme inhibitors. Cardiac catheterization was performed after written informed consent was obtained from each patient. All patients were followed for over 3.5 years or until death.

**Hemodynamic Assessments**

All patients initially underwent routine left and right diagnostic catheterization using a femoral approach. Diagnostic examinations contained pressure studies, coronary arteriography, and left ventriculography. After diagnostic procedures were undertaken, a 7F micromanometer-tipped catheter (Millar Industries, Houston, TX) was placed in the left ventricle. A 7F thermodilution floating catheter was placed in the pul-

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<th>Table 1. Patient Characteristics</th>
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<td><strong>Total number</strong></td>
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NYHA, New York Heart Association; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction.
monary artery. A 5F pacing catheter was advanced to the right atrium in patients with sinus rhythm and to the right ventricle in patients with atrial fibrillation. Left ventricular pressure, the first derivatives of left ventricular pressure (dP/dt), and pulmonary artery pressure were recorded on a chart recorder during this study. Electrocardiography of surface limb leads were simultaneously traced.

**Definitions of Mechanical Alternans**

Mechanical alternans was detected by direct pressure measurement. Electrical alternans was evaluated from 2 surface limb leads, II and aVF. Several terms relating to mechanical alternans were defined as follows. A magnitude of pressure difference of the strong beat and the weak beat was defined as an alternating pressure. Large alternans indicated mechanical alternans having 10 mm Hg or more of an alternating pressure, which may be recognized by physical examinations. Small alternans indicated an alternating pressure less than 10 mm Hg. The term *sustained alternans* was defined when constant alternating pressure exceeding 4 mm Hg continued beyond 20 beats. When alternating pressure gradually tapered and ultimately disappeared until 20 beats, the term *decay alternans* was used. Only sustained alternans was included in this study; decay alternans was neglected. Biventricular alternans was detected by a simultaneous pressure recording of the left ventricle and the pulmonary artery. Concordant alternans indicated that both ventricular strong or weak beats coincided. When a strong beat of 1 ventricle coincided with a weak beat of the opposite ventricle, the term *discordant alternans* was used. The *phase reversal point* was defined as a coupling interval of a premature beat that showed phase reversal effects on mechanical alternans. Demonstrable traces of mechanical alternans are presented in Fig. 1. The left panel shows aortic pressure of a female patient with idiopathic dilated cardiomyopathy under sinus rhythm. Her alternating pressure was extremely large, and her peripheral pulse rate was half the heart rate. The right panel shows a left ventricular pressure tracing of a male patient with idiopathic dilated cardiomyopathy under atrial pacing of 110 bpm. His left ventricular pressure and pulmonary artery pressure showed concordant alternans, and the positive and the negative dP/dt of left ventricular pressure also showed alternating changes.

**Rapid Pacing**

An abrupt tachycardia of extremely rapid heart rates has been shown to be related to the initiation of mechanical alternans in clinical and experimental observations. In this study, we tested physiologic tachycardia and did

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![Fig. 1](image-url)  
**Fig. 1.** Demonstrable records of mechanical alternans. (A) Aortic pressure tracing of a female patient with idiopathic dilated cardiomyopathy. Alternating pressure was 32 mm Hg. ST-T electrical alternans was also detectable. (B) Tracing of left ventricular pressure and the first pressure derivatives from a male patient with idiopathic dilated cardiomyopathy. Both positive and negative dP/dt showed alternating changes with left ventricular pressure. Pulmonary artery pressure exhibited concordant alternans with the left ventricle. AO, aortic pressure; LA, left atrial pressure; LV, left ventricular pressure; PA, pulmonary arterial pressure; S, strong beat; W, weak beat.
not test extremely rapid heart rates. After diagnostic catheterization, provocation of mechanical alternans by right atrial pacing was carried out. The pacing rate was 110 bpm. In patients with atrial fibrillation, right ventricular pacing of 110 per minute was performed.

**Intravenous Dobutamine**

The effects of inotropic agents on the appearance of mechanical alternans were investigated in this study. Previous experimental observations suggested that impaired intracellular calcium cycling is essential in the prevalence of mechanical alternans. Therefore, in this study, effects of dobutamine that increase intracellular calcium cycling were tested. Dobutamine was intravenously infused with an upward titration of the infusion rate at 5-minute intervals. Stepwise dobutamine loading was initiated at a dose of 2 µg/kg/min, then the dose was increased to 4 and 8 µg/kg/min. Three minutes after the start of dobutamine infusion, a constant pacing of 110 per minute was started, and hemodynamic parameters were measured at 5 minutes after dobutamine loading. All study protocols were approved by the ethics committee of Niigata University, Niigata, Japan.

**Statistical Analysis**

Data are presented as mean ± SD. The unpaired Student t test was used to calculate the statistical differences between 2 groups. Differences were considered significant at \( P < .05 \). Relations between pressure alternans and dP/dt alternans were analyzed using the partial correlation coefficients.

**Results**

**Frequency of Mechanical Alternans**

The prevalence of mechanical alternans in patients with chronic heart failure was investigated under the basal condition, rapid pacing of 110 per minute, and stepwise dobutamine loading. Under the basal condition, 7 out of 35 patients with sinus rhythm (20%) showed mechanical alternans (Fig. 2). Six patients (17%) showed large alternans. Rapid pacing provoked mechanical alternans in another 15 patients with sinus rhythm and in another 10 of 16 patients with atrial fibrillation. Five patients with large alternans at rest were not enrolled in further studies. Accordingly, 27 of 46 patients (59%) showed mechanical alternans under rapid pacing. Dobutamine loading at a dose of 2 µg/kg/min was tested in 40 patients. Nineteen patients (48%) showed mechanical alternans. A dose of 4 µg/kg/min of dobutamine was tested in 38 patients, and 23 patients (61%) showed mechanical alternans. Low doses of dobutamine, either 2 or 4 µg/kg/min, induced mechanical alternans in 8 patients for the first time, who did not show mechanical alternans under either the basal condition or rapid pacing. Subsequently, a high dose of dobutamine at 8 µg/kg/min was tested and data, which were available for evaluation, were collected from only 28 patients because of tachycardia exceeding pacing rates or frequent premature beats. Mechanical alternans was observed in 8 patients (28%). Nobody showed for the first time, mechanical alternans under the high dose of dobutamine. Consequently, 40 patients (78%) showed mechanical alternans under either condition, basal, rapid pacing, or low doses of dobutamine. Thus, rapid pacing and low doses of dobutamine were frequently able to provoke mechanical alternans in patients with chronic heart failure, and high doses of dobutamine eliminated mechanical alternans. Large alternans was still rare under the provocation procedures in patients with chronic heart failure.

**Alternans of the First Pressure Derivatives**

During sustained mechanical alternans, oscillation of the positive and the negative dP/dt of left ventricular pressure was investigated. When the alternating pressure was large, both positive and negative dP/dt showed alternating changes. When the alternating pressure was small, positive dP/dt showed alternating strong and weak beats, but negative dP/dt was occasionally constant. The relation between the magnitude of alternating left ventricular pressure and the magnitude of alternating dP/dt of each patient at maximum mechanical alternans are plotted. Pressure alternans was related more linearly to positive dP/dt than negative dP/dt. Positive dP/dt oscillated with mechanical alternans in all patients (Fig. 3).
6 patients, mechanical alternans was sustained without oscillation of negative dP/dt (Fig. 4). As left ventricular dP/dt is influenced by preload and afterload, strict assessment of contractility and relaxation property during mechanical alternans may be incomplete in this study. Otherwise, our observation implies that mechanical alternans depends not on the relaxation property of a prior beat but on a contractile property during the isovolumic contraction phase.

**Biventricular Alternans**

The appearance of biventricular alternans was investigated in 35 patients by simultaneous pressure recordings of the pulmonary artery and the left ventricle. Most patients with chronic heart failure showed single ventricular alternans of the left ventricle (24 of 35, 69%). Biventricular alternans was observed in 11 patients (31%), and 10 of the 11 patients showed concordant alternans of both ventricles. In a male patient with idiopathic dilated cardiomyopathy, biventricular discordant alternans was detected. In this case, both concordant and discordant alternans were observed during a study, and concordant alternans changed into discordant alternans after a premature ventricular contraction. The mean right atrial pressure and the mean pulmonary arterial pressure were constant before and after this transformation of mechanical alternans. These observations imply that mechanical alternans of the left ventricle is independent of right ventricular stroke volume.

**Effects of Premature Beats**

Effects of premature beats on mechanical alternans were investigated. A premature beat, either supraventricular or ventricular, which appeared during a normal pulse without alternans, frequently provoked decay mechanical alternans and sometimes provoked sustained alternans in patients with chronic heart failure. A premature beat after a strong beat during sustained mechanical alternans always exaggerated alternating pressure. However, a premature beat after a weak beat expressed different effects on mechanical alternans according to the coupling intervals. A premature beat with a relatively long coupling interval after a weak beat attenuated alternating pressure. A premature beat with a proper coupling interval, that is a phase reversal point, after a weak beat diminished mechanical alternans. A premature beat with more shorter coupling intervals reversed the alternating strong-weak phase and rather exaggerated the alternating pressure.

**Mechanical Alternans and Clinical Characteristics**

Clinical characteristics of patients who showed mechanical alternans under either rest, mild tachycardia, or low doses of dobutamine (n = 40) were compared with those of patients without alternans under any conditions (n = 11) (Table 2). Patients with mechanical alternans had a higher score for the New York Heart Association functional class than those without. The left ventricular end-diastolic pressure and the pulmonary capillary wedge pressure were higher in patients with alternans than those without. The cardiac indices were not different between both groups. The left ventricular end-diastolic volume indices and end-systolic volume indices of patients with mechanical alternans were significantly larger than those of the patients without. The left ventricular ejection fraction in patients with alternans was lower than those without. There were, in this study, 8 patients with preserved systolic function whose left ventricular ejection fraction were over 45%. Three of these patients showed mechanical alternans, and 5 patients did not
show. Although there was no difference in the total mortality, death from heart failure was more frequent in patients with mechanical alternans.

**Discussion**

Until now, many observations concerning mechanical alterations have been reported, but both mechanisms and clinical implications of this phenomenon are still unknown. In this report, we showed a few unique findings concerning mechanical alternans of patients with chronic heart failure. The first is that mechanical alternans is rare at the resting condition, and its prevalence increases dramatically by physiologic tachycardia and low doses of β-adrenoceptor stimulants. The next is that mechanical alternans is always accompanied by alternating changes of positive dP/dt and is able to continue without oscillation of negative dP/dt.

The precise prevalence of mechanical alternans in patients with chronic heart failure has been unknown. Hada et al (22) investigated the frequency of mechanical alternans in 100 patients with dilated cardiomyopathy using echocardiography. They found sustained alternans in 10 patients and decay alternans in another 7 patients. Their conclusion was that there was no difference in the severity of disease in patients with mechanical alternans compared with those without. Schaefer et al (23) reported the prevalence of mechanical alternans in 104 patients with miscellaneous heart diseases by direct pressure measurement. The study used rapid atrial pacing as a provocation maneuver of mechanical alternans. Overall, 29 patients developed mechanical alternans, containing both decay and sustained, under either the basal condition or rapid atrial pacing. Our study included only patients with chronic heart failure; focused on only sustained alternans; detected it by a direct pressure recording of the left ventricle simultaneously with the first pressure derivatives; and used mild, maybe physiologic, provocation procedures. Many physicians have felt that pulsus alternans must be strictly related to heart failure and to a poor prognosis. However, there is no systematic study concerning these points until now (21). This study showed that the prevalence of sustained alternans under physiologic stimulation was associated with the severity of left ventricular dysfunction.

Several theories have been proposed as the cause of mechanical alternans. Mechanical alternans has been initially considered to occur from alternating ventricular filling patterns depending on the Frank-Starling mechanism (24). However, a regional discordant alternans of the left ventricle had been reported (25). Experimental studies have also shown that mechanical alternans can be provoked in the isometric contraction models under constant preload (13,14). These findings can deny the possibility of the Frank-Starling mechanism as a cause.

An incomplete relaxation theory has been formulated by the observation that a weak beat came out after a small end-diastolic volume with high end-diastolic pressure, and a strong beat began from a large end-diastolic volume with low end-diastolic pressure in some experimental models (26–28). However, this was not a rule in this study of human mechanical alternans. A strong beat appeared after various end-diastolic pressures, higher or the same as, and occasionally lower compared with a weak beat. The absolute value of the minimum negative dP/dt of strong beats was larger than that of weak beats.

Partial asystole of the left ventricle has been considered to be a cause of mechanical alternans (29).

| Table 2. Comparison of Clinical Characteristics, Cardiac Function, and Prognosis Between Patients With and Without Mechanical Alternans |
|---------------|----------------|----------------|----------------|
| Number        | 40             | 11             | Statistical Difference |
| Men/women     | 31/9           | 7/4            | NS             |
| Age (yr)      | 48.6 ± 13.2    | 48.2 ± 14.3    | NS             |
| NYHA 1        | 1 (3%)         | 2 (18%)        | P < .003       |
|              | 2 (52%)        | 8 (73%)        | P < .0003      |
|              | 18 (45%)       | 1 (9%)         | P < .02        |
| LVEDVI (mL/m²) | 141.7 ± 44.5   | 110.4 ± 19.9   | P < .003       |
| LVESVI (mL/m²)| 96.5 ± 40.1    | 60.9 ± 18.3    | P < .005       |
| LVEF (%)      | 33.3 ± 10.2    | 45.3 ± 11.5    | NS             |
| LVEDP (mm Hg) | 9.6 ± 6.8      | 4.7 ± 2.8      | P < .002       |
| PCW (mm Hg)   | 9.6 ± 6.2      | 6.2 ± 2.1      | P < .005       |
| CI (L/min/m²) | 2.7 ± 0.8      | 2.8 ± 0.6      | NS             |
| Mortality     | 10 (25%)       | 2 (18%)        | NS             |
| Death of heart failure | 7 | 0 | NS |
| Sudden death  | 3              | 1              |                |
| Noncardiac death | 0          | 1              |                |

NYHA, New York Heart Association; LVEDP, left ventricular end-diastolic pressure; PCW, pulmonary capillary wedge pressure; CI, cardiac index; NS, not significant.
mechanical alternans of patients derived from a partial asystole, alternating changes of the QRS morphology would be observed on electrocardiography. Additionally, as strong beats derived from full activation of the left ventricle by this theory, it would show the same intensity as the normal pulse without mechanical alternans. None of the 40 patients showed alternating changes of the QRS morphology during mechanical alternans in this study. The intensity of normal beats was just a middle value between strong beats and weak beats. Strong beats were always more intense than normal beats in this study. Accordingly, the partial asystole theory is unlikely.

The primary oscillation of mechanical alternans may exist in the action potential duration (30). If the oscillation of the action potential duration is the primary event, this form of mechanical alternans should be accompanied by ST-T electrical alternans and alternating changes of left ventricular relaxation property. From our study, ST-T electrical alternans was detected in only 3 out of 40 patients with sustained mechanical alternans. During mechanical alternans, alternating changes of positive dP/dt was more evident than alternating changes of negative dP/dt. Therefore, the theory of alternating action potential duration is unlikely.

Oscillation of afterload may be another potential origin of mechanical alternans. From our observation, alternating change of positive dP/dt was evident during mechanical alternans. Positive dP/dt is a parameter of myocardial contractility during the isovolumetric contraction time, before opening of aortic valve. In a few patients with large mechanical alternans, weak beats could not open the aortic valve (total alternans). Accordingly, primary origin of mechanical alternans seems to exist on the isovolumetric contraction time or more before.

Several experimental studies showed that the primary event of mechanical alternans was alternating amounts of Ca^{2+} sparks from the sarcoplasmic reticulum (9,14,15,31–34). This form of mechanical alternans showed heart rate dependency. In this study, some features of human mechanical alternans produced by premature beats agreed with theoretical mechanical alternans depending on Ca^{2+} sparks (31,35). However, we cannot explain the reason why low doses of dobutamine provoked mechanical alternans. Ca^{2+} sparks alternans leads to the oscillation of the initial tension development of myocardium. Alternating changes of cytosolic Ca^{2+} amounts can influence the calcium-dependent ion currents, which could subsequently lead to ST-T electrical alternans (36,37). Because direct evidence of Ca^{2+} sparks alternans could not be obtained in this study, further study will be necessary.

Mechanical alternans is rare under a resting condition in patients with chronic heart failure, and its prevalence increases dramatically under physiologic tachycardia or mild β-adrenergic stimulation. Mechanical alternans is more prevalent in patients with severe left ventricular dysfunction. Although the precise mechanisms of mechanical alternans is still uncertain, its origin may depend on the abnormal Ca^{2+} handling in failing myocardium.

References