Assessment of Length-dependent Regulation of Myocardial Function in Coronary Surgery Patients Using Transmitral Flow Velocity Patterns

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**Background:** In a subset of coronary surgery patients, a transient increase in cardiac load by leg elevation resulted in a decrease in maximal rate of pressure development (dP/dt \(_{\text{max}}\)) and a major increase in end-diastolic pressure (EDP). This impairment of left ventricular (LV) function appeared to be related to a deficient length-dependent regulation of myocardial function. The present study investigated whether analysis of transmitral flow patterns with transesophageal echocardiography constituted a noninvasive method to identify these patients.

**Methods:** High-fidelity LV pressure tracings and transmitral flow signals were obtained in 50 coronary surgery patients during an increase in cardiac load by leg elevation. Using linear regression analysis, changes in transmitral E-wave velocity and deceleration time (DT) were related to changes in dP/dt \(_{\text{max}}\) and EDP.

**Results:** Changes in dP/dt \(_{\text{max}}\) with leg elevation were closely related to corresponding changes in E-wave velocity (r = 0.81; P < 0.001) and to changes in DT (r = 0.78; P < 0.001). Similarly, changes in EDP were related to changes in E-wave velocity (r = 0.83; P < 0.001) and to changes in DT (r = 0.84; P < 0.001). The decrease in dP/dt \(_{\text{max}}\) and the major increase in EDP in some patients was associated with an increase in E-wave velocity and a decrease in DT, indicating development of a restrictive LV filling pattern.

**Conclusions:** Impairment of LV function with leg elevation was associated with the development of a restrictive transmitral filling pattern. Analysis of transmitral flow patterns by means of transesophageal echocardiography therefore allowed noninvasive identification of a subset of coronary surgery patients with impaired length-dependent regulation of LV function. (Key words: Contraction; echocardiography; relaxation.)

MITRAL flow velocity patterns have been increasingly used to assess left ventricular (LV) filling and diastolic function.1–5 Two distinct mitral flow velocity profiles (MFVPs) were identified that are associated with impaired ventricular relaxation and with a restrictive LV filling pattern.4,5 Recent studies showed that the MFVPs predicted survival in various cardiac conditions.6–8 Additional loading interventions allowed distinction between a reversible and a nonreversible form of restrictive LV filling. A more favorable outcome was observed when baseline MFVP was nonrestrictive or when a restrictive MFVP could be reverted by loading manipulations. In patients with a stable nonrestrictive MFVP, cardiac event rate was 6%. In patients with a reversible restrictive MFVP, cardiac event rate was 19%, and this rate amounted to 51% in patients with an irreversible restrictive MFVP.9 Despite its potential value, little is known about a possible role for MFVP analysis in the dynamic assessment of cardiac function during the perioperative period. It was previously shown in 10 patients undergoing coronary surgery that alterations in loading conditions altered transmitral flow profiles.10 Analysis of MFVP during an alteration in ventricular loading conditions may therefore yield additional information on LV functional reserve in the perioperative period.
In coronary surgery patients, evaluation of the effects of an increase in cardiac load by leg elevation allowed a dynamic assessment of LV functional reserve with identification of a subgroup of patients with impaired length-dependent regulation of myocardial function. These patients typically responded to leg elevation with a decrease in stroke volume and maximal rate of pressure development (dP/dt\text{max}), a delayed myocardial relaxation with enhanced load dependence of LV pressure decrease and a marked increase in LV end-diastolic pressure.\textsuperscript{11,12} Both impaired myocardial relaxation and increased LV filling pressures affect MFVP in a specific but opposite way (fig. 1). Impaired myocardial relaxation is characterized by a decrease in E-wave velocity, a prolongation of deceleration time, and a decrease in peak early and atrial flow velocity (E/A ratio). A restrictive filling pattern with elevated LV filling pressures, on the contrary, is associated with an increased E-wave velocity, a shortened deceleration time, and an increased E/A ratio.\textsuperscript{4,5} Not all MFVPs fit nicely into these two patterns. There is a wide spectrum of patterns depending on the underlying pathophysiologic and hemodynamic status.

Based on these different data, we hypothesized that the changes in MFVP during an alteration in loading conditions would give an indication on LV functional reserve. More specifically, analysis of the MFVP would indicate whether impairment of myocardial relaxation or instead increased LV filling pressures primarily affected
the LV filling pattern in patients with length-dependent impairment in myocardial function.

The present study therefore aimed to investigate how transmitral flow signals were altered when cardiac load was increased and whether the response to leg elevation was different in patients who developed length-dependent impairment of LV function. The clinical implication of this experimental question was to determine whether analysis of transmitral flow signals would constitute a noninvasive method for identifying patients with a deficient length-dependent regulation of LV function.

Methods

Patient Population

The study was approved by the Institutional Ethical Committee, and written informed consent was obtained. The study was performed on 50 patients with a preoperative ejection fraction > 40% who were scheduled for elective coronary bypass surgery. Patients undergoing repeat coronary surgery, concurrent valve repair, or aneurysm resection were excluded. Patients with unstable angina pectoris or concomitant valvular disease were also excluded. None of the patients included had mitral regurgitation.

Experimental Preparation

Experimental preparation has been described in detail previously.\(^{11,12}\) Transmitral flow data were acquired using a biplane 5-MHz esophageal ultrasound probe (Aloka UST-5233-S) connected to an SSD-830 Aloka echocardiographic unit (Tokyo, Japan). A four-chamber view was obtained, and the pulsed Doppler sample volume was placed at the center of the level of the mitral anulus. A sterilized, pre-zeroed electronic tipmanometer (MTCP3Fc catheter; Dräger Medical Electronics, Best, The Netherlands; frequency response = 100 KHz) was positioned in the LV cavity through the apical dimple. The catheter was connected to a Hewlett Packard monitor (HP78342A; Brussels, Belgium). Zero and gain setting of the tipmanometer were checked against a high-fidelity pressure gauge (Druck Limited, Leicester, United Kingdom) after removal.

Experimental Protocols

The present study aimed to perform a dynamic assessment of transmitral Doppler flow signals during an increase in cardiac load by elevation of the legs. The effects of leg elevation on LV pressure data were compared with the effects on transmitral flow data. Measurements were obtained with the ventilation suspended at end expiration. Consecutive electrocardiographic, LV pressure tracings, and pulmonary capillary wedge pressure (PCWP) tracings were recorded during an increase of systolic and diastolic LV pressures obtained by raising the caudal part of the surgical table by 45°, resulting in raising of the legs. This maneuver resulted in a rapid beat-to-beat increase in LV pressures. Care was taken to have at least 15 consecutive beats for analysis. The output signals of the pressure transducer system were digitally recorded together with the electrocardiographic signals at 1-ms intervals (Codas, DataQ, Akron, OH). Transmitral Doppler signals were recorded on VHS videotape at a rate of 25 images per second before and at the end of leg elevation. At least five consecutive beats were recorded for averaging. Hemodynamic and Doppler data were analyzed offline. Doppler data were analyzed separately by two independent observers who were blinded from the hemodynamic measurements. Intraobserver variability was less than 3% for all measurements, whereas interobserver variability never exceeded 6% for any measurement.

Hemodynamic Measurements

End-diastolic pressure (EDP) was timed at the peak of the R wave on electrocardiogram. End-systolic pressure (ESP) corresponded to pressure at maximal rate of pressure decline (dP/dt\(_{\text{min}}\)). Isovolumic relaxation time was measured on the LV pressure tracing from dP/dt\(_{\text{min}}\) to a cutoff value of 10 mmHg above EDP. The time constant of isovolumic pressure decline (\(\tau\)) was calculated using pressure values from dP/dt\(_{\text{min}}\) to a cutoff value of 10 mmHg above EDP. The following equation was used: 
\[
\ln P_t = \ln P_0 - \text{time}/\tau \quad ^{13,14}
\]

Time constant, \(\tau\), was linearly fit to the corresponding ESP, and the slope, \(R\) (ms/mmHg), of this relation was calculated. \(R\) quantified changes in \(\tau\), induced by the change of end-systolic LVP and quantified afterload dependence of the rate of LVP decrease\(^{15}\) (fig. 2). At least 10 consecutive beats were taken for the calculation of \(R\). Sample correlation coefficients of the ESP–\(\tau\) relations yielded values of \(r > 0.93\) in all patients.

Doppler Measurements

Doppler measurements before and at the end of leg elevation were averaged over five consecutive cardiac cycles. The measurements included E/A ratio, early and atrial velocity time integral, and total velocity time integral. The atrial filling fraction was defined as the ratio of
the integral of the A wave to the total integral of the mitral flow velocity curve. Deceleration time was measured from the peak of the E wave to the time when the extrapolated descent of the E wave intercepted the zero baseline.

**Statistical Analysis**

Data before and after leg elevation were compared using two-way analysis of variance for repeated measurements. Posttest analysis was performed using the Bonferroni–Dunn test. Changes in hemodynamic parameters and Doppler data were related using linear regression analysis computing Pearson’s correlation coefficient. Data were reported as mean ± SD. Statistical significance was set at $P < 0.05$.

**Results**

Preoperative and intraoperative data of the patients included in the study are summarized in table 1. Table 2 displays the hemodynamic data at baseline and at the end of leg elevation. Heart rate remained unchanged, and EDP and PCWP increased with leg elevation. A close relation was observed between changes in EDP and changes in mean PCWP ($r = 0.87; P < 0.001$). Leg elevation increased peak LVP with $14 ± 5$ mmHg. Mean $dP/dt_{\text{max}}$ remained unchanged, but a variable response was observed in the individual values: an increase in

<table>
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<th>Table 1. Preoperative and Intraoperative Data</th>
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<td>Preoperative data</td>
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<td>Male/female</td>
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<td>Age (yr)</td>
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<td>Length (cm)</td>
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<td>BSA (m²)</td>
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<td>Ejection fraction (%)</td>
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<td>Medication</td>
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<tr>
<td>Nitrates</td>
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<td>$\beta$-Blocking drugs</td>
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<td>Ca-channel blocking drugs</td>
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<tr>
<td>ACE inhibitors</td>
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<tr>
<td>Other</td>
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<td>Intraoperative data</td>
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<tr>
<td>No. of grafts (range)</td>
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<td>Aortic cross-clamp time (min)</td>
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<td>CPB time (min)</td>
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Data are no of patients and mean ± SD.

<table>
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<tr>
<th>Table 2. Hemodynamic and Transmitral Flow Data before (Baseline) and after Leg Elevation (N = 50)</th>
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Values are mean ± SD. $dP/dt_{\text{max}}$ = maximal rate of pressure development; PCWP = pulmonary capillary wedge pressure; LV = left ventricular.

* Statistically significant from baseline for $P < 0.05$.  

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tion time decreased, indicating development of a restrictive LV filling pattern. Patients who developed an increase in dP/dt_max showed only a slight decrease or no change in E-wave velocity with no change or a slight increase in deceleration time.

The effects of leg elevation on myocardial relaxation were evaluated by analysis of changes in isovolumic relaxation time, changes in τ, and by analysis of R. R is the slope of the relation between the changes in τ and the corresponding changes in ESP during leg elevation and quantifies load-dependence of rate of relaxation. A positive value means that τ increases (slowing of LV relaxation) with the increase in ESP, whereas a negative value means that τ decreases (acceleration of LV relaxation) with the increase in ESP (fig. 2). Isovolumic relaxation time remained unchanged. The mean value of τ increased, but the individual response was variable. Mean R was 0.33 ± 0.55 ms/mmHg with an important individual variability. A close relation was observed between the individual R values and the corresponding changes in peak E-wave velocity and deceleration time with leg elevation (fig. 4). Patients with the most pronounced load-dependence of rate of relaxation (slowing of relaxation with increased load) showed an increase in peak E-wave velocity and a decrease in deceleration time with leg elevation.

A close relation was also observed between changes in peak E-wave velocity and the corresponding changes in
EDP. Similarly, changes in deceleration time with leg elevation were closely related to the changes in EDP (fig. 5). The patients who developed a major increase in EDP with leg elevation showed an increase in peak E-wave velocity and a decrease in deceleration time, indicating development of a restrictive filling pattern. Changes in mean PCWP were also related to corresponding changes in peak E-wave velocity and deceleration time, indicating development of a restrictive filling pattern (filled squares).

**Discussion**

Although the prognostic value of Doppler echocardiography of mitral flow velocities has been assessed in different cardiac conditions, the potential benefit of this analysis in the perioperative period of cardiac surgery remained to be established. MFVPs reflect LV filling and are therefore used to assess diastolic function. MFVPs are also altered by changes in hemodynamic loading conditions. Nitroglycerin decreases PCWP with a concomitant decrease in peak E-wave velocity and an increase in deceleration time. Administration of fluids, on the other hand, increases PCWP together with an increase in peak E-wave velocity and a decrease in deceleration time. Analysis of changes in MFVP with manipulations of LV loading conditions might therefore yield additional information on individual myocardial functional reserve.

The present data indicated that analysis of changes in E-wave velocity and deceleration time during a dynamic change in cardiac load with leg elevation allowed identification of patients with a deficient length-dependent regulation of myocardial function. These patients typically responded with a decrease in dP/dt max, a high increase in EDP, and an increased load-dependence of LV pressure decrease. In these particular patients, the transmitral flow signal showed the development of a restrictive filling pattern with an increase in E-wave velocity and a decrease in deceleration time. Changes in PCWP also closely resembled changes in EDP with leg elevation and therefore constituted an alternative way to identify impaired length-dependent regulation.

Transmitral flow reflects the left atrial-LV pressure gradient. This pressure gradient depends on the left atrial opening pressure (which depends on left atrial volume and compliance), LV relaxation rate, LV compliance, and LV volume. Because of this multiplicity of determinants of left atrial-LV pressure gradients, alterations in transmitral filling patterns may be produced by a variety of physiologic and pathologic mechanisms. Accordingly, mitral flow patterns may vary greatly, not only within the same patient, but also among different patients, certainly when variations in loading conditions occur either by drug interventions or by postural changes.

Compared with normal values, mean peak E-wave velocity was decreased and mean A-wave velocity was slightly increased. Accordingly, E/A ratio was less than 1, and mean deceleration time was increased. These mean baseline data indicated that some patients already had impaired relaxation on their baseline tracings. Impairment of relaxation was also confirmed by the higher values of the time constant of isovolumic relaxation time ($\tau$) in these patients.
Leg elevation did not significantly affect transmirtal flow patterns in the majority of patients. Only the patients who developed length-dependent impairment of myocardial function developed a restrictive filling pattern with an increased E-wave velocity and a decrease in deceleration time. The effects of the slower myocardial relaxation on transmirtal flow patterns in these patients (higher values of \( \tau \) and \( R \) [increased load-dependence of myocardial relaxation]) were probably masked by the development of the restrictive filling pattern. This indicated that in these patients, the effects of increased LV EDP on transmirtal LV filling patterns outweighed the effects of impairment of relaxation. Development of a restrictive filling pattern with leg elevation could not be related to baseline transmirtal flow patterns.

Several methodologic aspects deserve attention. Transmirtal flow velocities were recorded from a Doppler sample volume positioned at the level of the mitral anulus. This location was chosen because it provides a site where the change in diastolic cross-sectional area is minimal, and velocity is therefore related to volumetric changes. However, location of the sample volume at this site tends to decrease early (E wave) and increase late (A wave) mitral flow velocities compared with signals obtained at the mitral tips. Respiration and changes in ventricular preload and afterload—all of which occur during positive pressure ventilation—may dramatically alter transmirtal flow patterns. Therefore, measurements were obtained with the ventilation suspended at end expiration. Moreover, respiration and changes in ventricular preload and afterload—all of which occur during positive pressure ventilation—may dramatically alter transmirtal flow patterns. Therefore, measurements were obtained with the ventilation suspended at end expiration. Transmirtal flow patterns are also affected by heart rate. Increased heart rate results in an encroachment of the deceleration phase into the A wave and an augmentation of the velocity of this late diastolic filling wave. In the present study population, leg elevation did not affect heart rate, excluding this factor as a possible confounding element.

Left ventricular filling pressures were assessed by direct intraventricular EDP and by mean PCWP measurements. A close relation was observed with leg elevation between the changes in LV EDP and the corresponding changes in PCWP. Increasing evidence indicates a possible role for transmirtal flow velocity analysis in the assessment of LV EDP and PCWP. In the present observations, changes in PCWP with leg elevation were also related to corresponding changes in peak E-wave velocity and deceleration time.

Data were obtained in anesthetized patients. This implies that neurohumoral reflexes, including those mediating cardiac function, may have been blunted or altered with anesthesia. Another point is that the data were obtained in the presence of an open chest and open pericardium. The absence of pericardium may have over-dilated the heart because a rightward shift of the end-diastolic pressure–dimension relation has been shown after pericardiectomy.

The results of the present study suggested the presence of two distinct groups of patients who responded differently to leg elevation. Figure 6 projects the changes with leg elevation in the present study on a total group of 250 patients of previous observations. It appears that in the wide array of responses, no patient of the present study population projected in the transition zone (\( \Delta \text{dP/dt}_{\text{max}}: 0 \text{ to } -50 \text{ mmHg/s; } \Delta \text{EDP: approximately 10 mmHg} \)). Further investigation must therefore elucidate whether the effects of leg elevation on MFVP constitute a continuous array of responses or instead allow for subdivision in two groups. In addition, all patients in the present study had a preoperative ejection fraction of more than 40%. Further studies must evaluate whether the present observations are also valid for patients with a lower baseline ejection fraction.

In conclusion, in patients with impaired length-dependent regulation of myocardial function, an increase in cardiac load with leg elevation resulted in an increase in E-wave velocity and a decrease in deceleration time. These changes indicated that the effects of the increase in LV EDP on trans-MFVP observed in these patients outweighed the effects of the impaired relaxation, resulting in a restrictive filling pattern.
References


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