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Noninvasive Estimation of the Rate of Relaxation by the Analysis of Intraventricular Pressure Gradients

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Background—During late ejection, myocardial relaxation causes systolic flow to decelerate and stop, and this phenomenon is coupled with the generation of a pressure gradient inside the left ventricle (LV). We hypothesized that the peak reverse ejection intraventricular pressure difference (REIVPD) between the LV apex and the outflow tract could be a useful method to improve the assessment of LV relaxation using Doppler echocardiography.

Methods and Results—Three sets of animal experiments and 1 clinical study were designed. In 6 pigs, a close relationship between REIVPD and the intensity of the relaxation wave ($R_{rm} = 0.89$) was demonstrated using wave intensity analysis of high-fidelity pressure-volume-velocity data. In 19 animals, REIVPD sensitively detected modifications of the lusotropic state and closely correlated with the time constant of LV relaxation (τ) within animals ($R_{rm} = -0.93$). Load-dependence analysis in 5 pigs showed that REIVPD remained stable up to values of 35% to 40% acute preload reduction. Clinical validation was tested in 50 patients (23 with normal systolic function) undergoing simultaneous Doppler echocardiography and high-fidelity LV pressure measurements on the same beat. REIVPD and tissue Doppler mitral annulus velocity (e′) were independently related to τ, but the REIVPD · e′ product correlated better with τ than either variable separately (bootstrap-corrected correlation coefficients: $R = -0.84$ versus -0.71, and -0.70, respectively, $P < 0.05$). Area under the receiver operating characteristic curve to predict impaired relaxation ($\tau > 50$ ms) for e′ · REIVPD was 0.96 (95% confidence interval, 0.85 to 0.99).

Conclusions—The Doppler-derived REIVPD provides a sensitive, reliable, reproducible, and relatively load-independent index of the rate of LV relaxation. Combined with tissue Doppler measurements of longitudinal function, this method improves noninvasive assessment of LV relaxation in the clinical setting. (***Circ Cardiovasc Imaging***. 2011;4:94-104.)

Key Words: echocardiography ■ hemodynamics ■ imaging ■ pressure ■ diastole

More than one-third of patients with heart failure have normal left ventricular (LV) systolic function.[1] In these patients, symptoms are caused by impaired diastolic filling due to abnormal ventricular relaxation, impaired diastolic suction, increased myocardial stiffness, or a combination of these. Because classic clinical signs and symptoms are not enough to establish the diagnosis of heart failure with normal LV systolic function, the need of an objective evidence of diastolic dysfunction has been emphasized.[2] Doppler echocardiography is the technique used to assess relaxation in the clinical setting, and current guidelines recommend measuring early diastolic longitudinal lengthening velocity of the mitral annulus (e′ velocity) for this purpose. However, recent studies have demonstrated the limited accuracy of these Doppler-derived methods,[3] and a reliable noninvasive method to characterize the state of LV relaxation is still an unsolved issue.[4,5]

Clinical Perspective on p 104

At the chamber integration level, myocardial relaxation generates an expansion wave inside the LV that travels from the apex to the aorta decreasing pressure and causing ejection flow to decelerate and stop.[6] As anticipated by fluid-dynamic principles, flow deceleration is coupled to a reversed pressure gradient inside the ventricle, pressure becoming lower at the apex than at the LV outflow tract (LVOT) during the last third of ejection. On this background, we hypothesized that the reverse ejection intraventricular pressure difference (REIVPD) is determined by the rate of LV relaxation. Because ejection intraventricular pressure gradients can be

accurately measured by Doppler echocardiography,[7,8] this hypothesis could be the basis for a new method to measure the relaxation rate noninvasively.

The present study is designed to comprehensively assess the role of noninvasively measured REIVPDs to characterize LV relaxation. First, an animal high-fidelity pressure and conductance setup is used with a 3-fold purpose: (1) to validate the hypothesis of a direct relationship of REIVPDs with the phenomenon of relaxation using wave-intensity analysis (WIA); (2) to quantify the sensitivity of REIVPDs to experimentally induced changes in lusotropic state and test its correlation with the time constant of relaxation (τ) within animals; and (3) to analyze preload dependence of REIVPDs. Finally, in the clinical setting, the additional value of this new method to estimate τ is assessed in 50 patients undergoing simultaneous Doppler echocardiography and high-fidelity LV pressure measurements.

Methods

Both in animal and clinical studies, color Doppler and high-fidelity catheterization data were acquired simultaneously. To guarantee same-beat measurements of color Doppler and pressure data, a cross-correlation algorithm was applied on a synchronicity signal stored simultaneously on the ultrasound scanner and the signal acquisition system.[7,8]

Animal Experimental Protocols

Adult minipigs (weight, 60 ± 10 kg) were used for all experiments. Study protocols were approved by the local Institutional Animal Care Committee. Animals were preanesthetized with ketamine and xylazine and mechanically ventilated. Complete anesthesia and relaxation were maintained by propofol infusion (0.2 mg/kg/min) as well as repetitive boluses of pentobarbital (15 mg/kg i.v.+5 mg/kg/15 minutes) and pancuronium (0.2 mg/kg/15 minutes). Through the right carotid artery, a 5F pigtail 12-pole multielectrode conductance-pressure catheter (Millar Instruments, Houston, TX, or CD-Leycom, Zoetermeer, The Netherlands) was placed into the LV and connected to a dual-field conductance processor (Sigma 5DF, CD-Leycom). Catheter balance and calibration was performed as previously described.[8] Animals were euthanized at the end of all experiments.

Experimental Study 1: WIA

Six pigs underwent median sternotomy without opening the pericardium, and the heart was cradled. A snare was placed around the inferior vena cava for preload manipulation. Animals were studied at baseline (n=6), during dobutamine (1 to 10 μg/kg/min; n=5), and esmolol (25 to 200 μg/kg/min; n=3) infusions, as well as after left main coronary microembolization of polystyrene microspheres (mean diameter, 45 μm; Polysciences, Warrington, PA; n=2). Immediately after data acquisition, a transient caval occlusion was performed. This acquisition process was repeated 3 times for each state, waiting for stabilization periods >5 minutes. B-mode (4- and 2-chamber views) and color-Doppler M-mode (CDMM) images of LV outflow velocity were recorded in each hemodynamic state.

Experimental Study 2: Lusotropic Sensitivity

A total of 19 animals were used: (1) the 6 animals from study 1; (2) 7 animals in a closed-chest setup, undergoing esmolol and dobutamine infusion (same doses as above) as well as right ventricular pacing (100, 120, and 150 bpm); and (3) 6 open-chest closed-pericardium pigs undergoing left anterior descending coronary artery ligation (n=5) and/or volume overload (n=4; saline, 0.9% 500 to 1000 mL). Images for measuring flow propagation velocity (FPV) and septal and lateral mitral annulus pulsed-wave Doppler (e$'_{septal}$ and e$'_{lateral}$, respectively) were also obtained in the latter group.
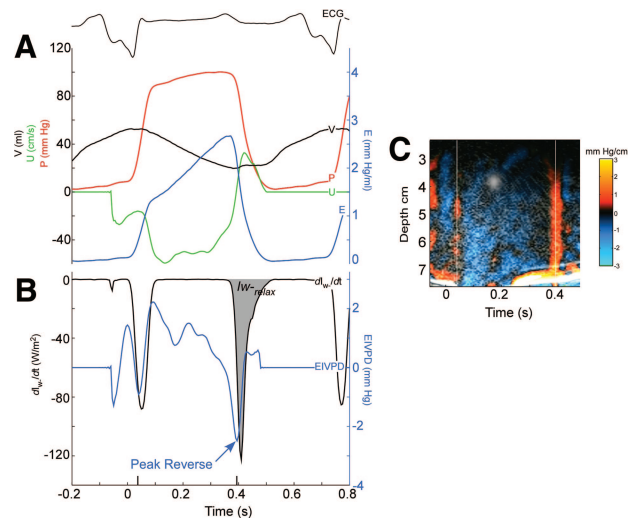

Figure 1. Example of WIA (experimental study 1). Simultaneous tracings are shown for ECG (top in black), LV volume (V, black, panel A), LV pressure (P, red, panel A), LVOT velocity (U, green, panel A), LV elastance (E, blue, panel A), the power of the aspirating relaxation wave (dl_w/dt, black, panel B), ejection intraventricular pressure difference (EIVPD, blue, panel B), and the 1-dimensional LV pressure gradient field (C). The energy of the aspirating wave ($Iw-_{relax}$) is represented by the shadowed area. Temporal markers are shown for ejection onset and end.

Experimental Study 3: Load Dependence

Five closed-chest pigs were studied during infusion of dobutamine and esmolol, at baseline, and during 10 seconds of caval occlusion.[8] Consecutive beat-to-beat data obtained during caval occlusion were used to assess the degree of preload dependence of REIVPDs and τ.

Clinical Study

Fifty patients in sinus rhythm undergoing left heart catheterization were included. Indications for the catheterization procedures were (1) ruling out coronary artery disease in patients with dilated cardiomyopathy (n=25), (2) chest pain of unknown etiology (n=8), and (3) non–ST-segment elevation acute coronary syndrome (n=17). In 27 patients, global systolic function was impaired (ejection fraction <50%). Significant coronary artery disease was demonstrated in 20 patients. All catheterization procedures were performed either through the left radial (n=37) or femoral approach (n=13), using a high-fidelity micromanometer 5F pig-tail catheter (Millar Instruments). ECG, pressure signals, and echocardiographic images were obtained simultaneously in left lateral decubitus position. The study protocol was approved by the local institutional review committee, and all subjects provided written informed consent for this study.

Echocardiographic Image Acquisition and Analysis

Broadband 2.0- to 4.0-MHz transducers were used either on a Sequoia C-256 (Siemens AG) or a Vivid-7 (General Electric Healthcare) system. LV volumes and ejection fraction were calculated using biplane Simpson method. Additional echo Doppler measurements, including transmitral E-wave velocity, mitral annulus e$'$ wave lengthening velocity (averaged values of septal and lateral annulus positions), and FPV were performed as recommended.[9]

Color Doppler M-mode images were obtained from the 5-chamber view.[7] The method for image processing has been previously reported[10] and validated to obtain the waveform of the LV apex–LVOT instantaneous pressure difference.[7] Briefly, if the M-mode cursor closely approximates a flow streamline, the spatiotemporal velocity distribution of a discrete blood sample is provided by the value of its corresponding pixel color: $v(s,t)$, where v represents velocity, s represents the linear dimension of the streamline, and t is
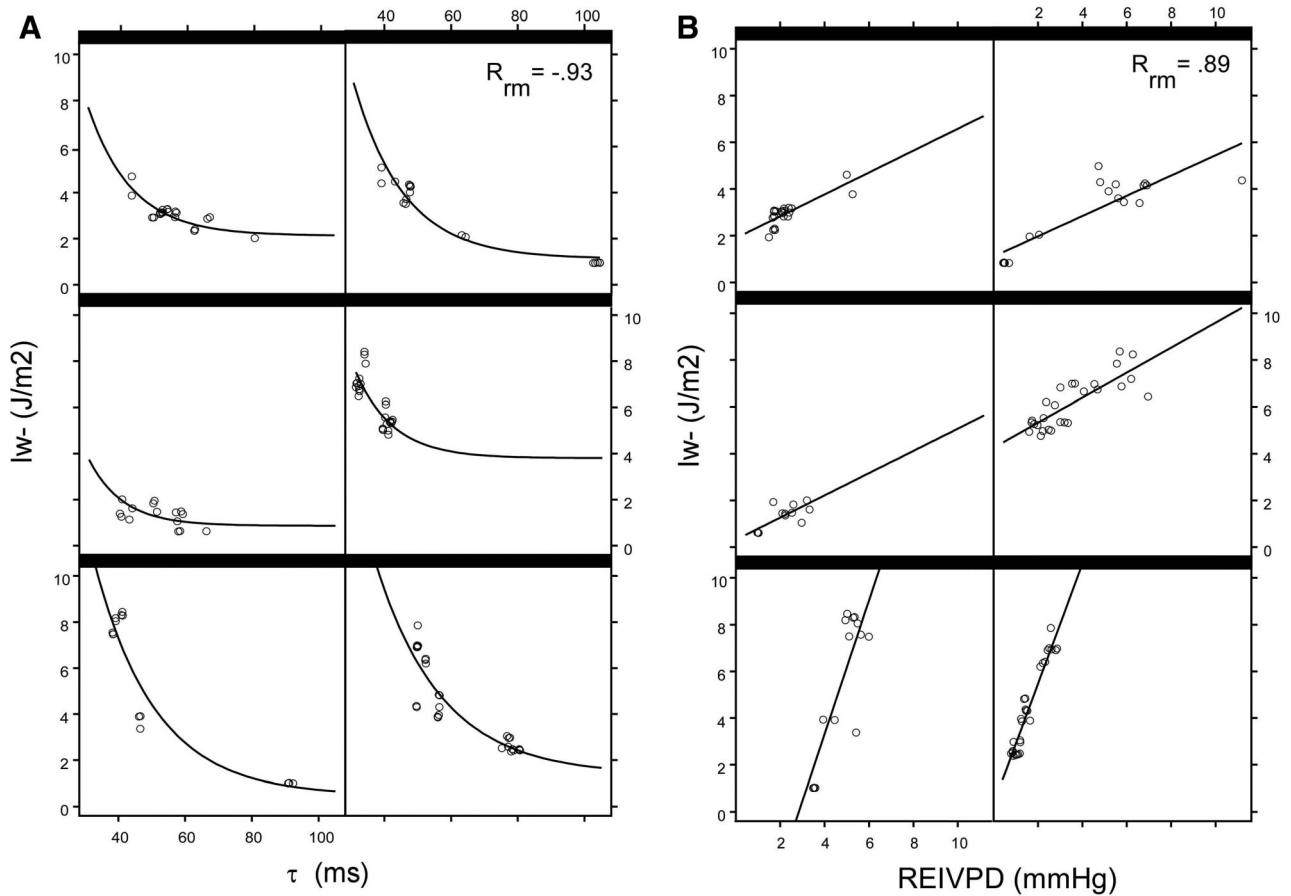
Figure 2. Results of the WIA (experimental study 1). A, Nonlinear relationship between the energy of the expansion wave ($Iw-_{relax}$) with the time constant of relaxation (τ) in each of the 6 animals, fitted to a nonlinear mixed-effects exponential model as $Iw-_{relax}=a+b \cdot e^{c \cdot t}$. B, Linear relationship between $Iw-_{relax}$ and REIVPD.

time. Thus, the color Doppler M-mode recording provides the data necessary to solve the Euler momentum equation:

$$\frac{\partial p}{\partial s}=-\rho \cdot \left(\frac{\partial v}{\partial t}+v \cdot \frac{\partial v}{\partial s}\right),$$

where p designates pressure and ρ is blood density. The first and second terms in the right side of the equation account for inertial and convective acceleration, respectively. The pressure difference curve is calculated by spatial integration between the apex and the LVOT of pressure gradient maps. From each curve, the systolic peak and reverse peak were automatically obtained and confirmed visually.

Intraobserver, interobserver, and beat-to-beat variabilities of REIVPD measurements (20 unselected patients referred for a conventional echocardiographic examination; independently and blindly acquired CDMM recordings) were 0.1±0.3 mm Hg (5±11%; $R_{ic}=0.99$), 0.2±0.6 mm Hg (6±24%; $R_{ic}=0.96$), and 0.2±0.3 mm Hg (4±15%; $R_{ic}=0.98$), respectively.

Pressure Data Analysis

All signals were digitized at 1000 Hz. To estimate τ, the zero asymptote model was adjusted using a nonlinear Levenberg-Marquardt fitting algorithm.[11] This method was chosen because it is less sensitive to noise at low pressure than logarithmic linearization.[12] Additionally, the nonzero asymptote ($\tau_{nonzero}$) and the logistic (τ_{logist}) models were fitted in the clinical study using the same method.[13] Beat-to-beat reproducibility of invasive methods was assessed from 2 consecutive beats from 20 patients. Values of τ, dP/dt, peak-systolic, and pre-A LV diastolic pressures were blindly computed for the same beat processed noninvasively.

Wave-Intensity Analysis

WIA was performed by combination of invasive and echo Doppler data, replicating previous methodology.[6] In a first step, ventricular elastance (E) was calculated as a function of time (t) by using simultaneous pressure (P) and volume (V) measurements provided by the conductance catheter as

$$E(t)=\frac{P(t)}{V(t)-V_0},$$

where V_0 is the zero pressure intercept calculated from the family of pressure-volume loops obtained during caval occlusion. Wave speed (c) was then calculated as

$$c(t)=\sqrt{\frac{E(t)\left(\frac{3}{2}V(t)\right)}{\rho}}.$$

The instantaneous power (per unit of cross-sectional area) of the expansion wave traveling from the LV ($dIw-$[W/m^2]) was calculated as

$$d(Iw-)/dt=(-4\rho)^{-1}(dP/dt-\rho cdU/dt)^2,$$

where dP/dt is the incremental difference in LV pressure during a 5-ms sampling interval, and dU is the difference in outflow velocity. For this purpose, U was measured by decoding color Doppler M-mode data at the level of the LVOT, as validated.[10] The total energy (per unit cross-sectional area) transported by the expansion wave during LV relaxation ($Iw-_{relax}$ [J/m^2]) was calculated as the integral under this part of d$Iw-$ waveform. Because LV inflow velocity was not considered for this analysis, $Iw-_{relax}$ did not include

Table 1.   Hemodynamic Data Obtained at Baseline and During Hemodynamic Interventions for Experimental Study 2

	Baseline	Esmolol	Dobutamine	Right Ventricular Pacing	Volume	Left Anterior Descending Artery Occlusion	Coronary Embolization
Animals, n	19	10	12	7	4	5	2
Beats, n	111	58	84	52	19	62	16
Heart rate, bpm	99 (94 to 105)	89 (83 to 95)†	108 (102 to 114)†	115 (109 to 122)†	90 (81 to 98)	88 (81 to 94)†	86 (77 to 94)†
LVSP, mm Hg	110 (99 to 120)	96 (86 to 107)†	129 (119 to 140)†	115 (104 to 126)	99 (86 to 111)†	88 (77 to 99)†	82 (70 to 95)†
LVEDP, mm Hg	13 (10 to 17)	13 (9 to 16)	18 (14 to 21)†	8 (2 to 15)	22 (18 to 26)†	15 (11 to 19)	23 (18 to 27)†
$(dP/dt)_{max}$, mm Hg/s	1866 (1586 to 2147)	1253 (940 to 1566)†	3598 (3297 to 3900)†	1982 (1647 to 2318)	1474 (1056 to 1893)	1492 (1151 to 1833)	675 (224 to 1126)†
$(dP/dt)_{min}$, mm Hg/s	−1824 (−2149 to −1499)	−1593 (−1928 to −1258)†	−2221 (−2553 to −1889)†	−2373 (−2714 to −2031)†	−1427 (−1799 to −1055)†	−1148 (−1494 to −801)†	−656 (−1040 to −272)†
τ, ms	45 (40 to 49)	49 (44 to 53)†	41 (37 to 46)†	41 (36 to 46)	56 (51 to 62)†	56 (51 to 61)†	79 (73 to 85)†
Peak REIVPD, mm Hg	3.5 (2.9 to 4.2)	2.4 (1.7 to 3.2)†	4.3 (3.6 to 5)†	3.1 (2.3 to 3.8)	2.6 (1.8 to 3.5)†	2.4 (1.7 to 3.2)†	2.1 (1.2 to 3.1)†
FPV, cm/s*	61 (40 to 83)	50 (24 to 76)			62 (41 to 84)	61 (39 to 83)	
e'_{Septum}, cm/s*	6 (5 to 7)	6 (4 to 8)			8 (6 to 9)	5 (4 to 6)†	
$e'_{Lateral}$, cm/s*	13 (10 to 15)	10 (7 to 13)†			12 (10 to 15)	9 (7 to 12)†	

LVSP indicates LV peak systolic pressure; LVEDP, LV end-diastolic pressure; FVP, flow propagation velocity.

Values are presented as fixed effects (95% confidence intervals).

†$P < 0.05$ versus baseline.

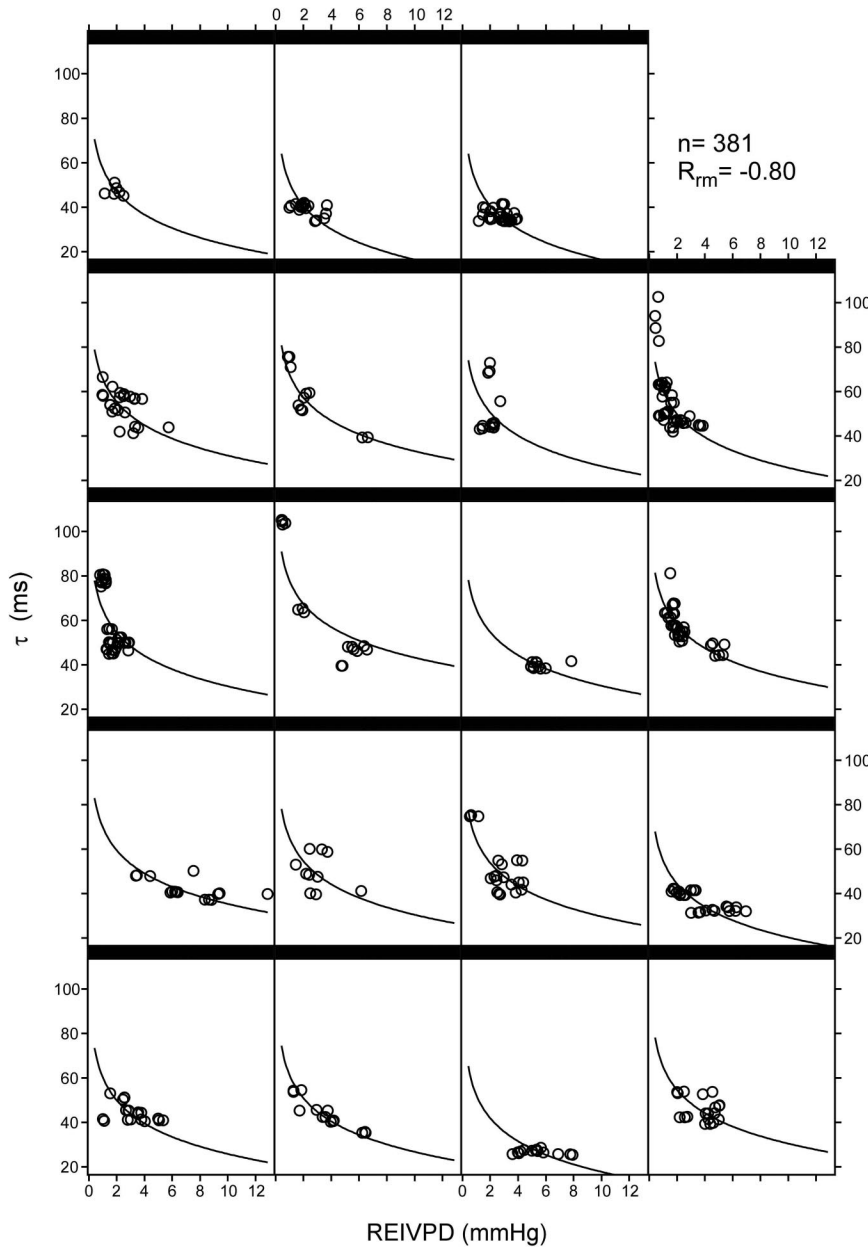*n=6 Animals each with the 4 hemodynamic states.

Figure 3. Results of the within-animal validation study (experimental study 2). Values are shown individually for each of the 19 animals. The linear fitting follows $\tau = A \cdot \log_e(\text{REIVPD}) + B$, where B is the random animal effect.

the additional ≈10% of energy of the expansion wave that extends into early filling.[6]

Statistical Analysis

Values are expressed as mean±standard deviation, except where indicated otherwise. Linear and nonlinear mixed-effects models (S-Plus v.8.0, Tibco) were used for analysis considering animals as random effects. Significant models were followed by simulation contrasts against baseline measurements.[14] For experimental study 1, $Iw-_{relax}$ was related to τ using an exponential model.[6] The association between $Iw-_{relax}$ and τ and REIVPD was addressed using within-animal correlation coefficients accounting for repeated measures (R_{rm}).[15] For animal studies 2 and 3, the effects of interventions on hemodynamic variables were calculated as the fixed-effect estimates and their 95% confidence intervals. Fixed-effect coefficients account for the mean expected values of variables once the source of variation resulting from the animal sampling random effect is omitted. For animal study 2, R_{rm} coefficients were calculated for the relationship between the noninvasive predictors and τ. In the clinical study, between-subject relationship was assessed using the Pearson correlation coefficient (R) after natural log transformation of REIVPD. Data from 3 consecutive beats were averaged. R coefficients were compared using Hotelling t tests. Variables from normal and abnormal ejection fraction clinical groups were compared using either a Welch-modified 2-sample t test or a χ^2 test, where appropriate. Adjusted R^2 values were used to compare multivariate regression models. Correlation coefficients in the clinical study were corrected to avoid overfitting by bootstrap validation of 1000 repetitions (R_{boot}). The Bland-Altman analysis and intraclass correlation coefficients (R_{ic}) were used to assess reproducibility. Receiver operating characteristic (ROC) curve analysis was performed using MedCalc. Values of $P<0.05$ were considered significant.

Results

Experimental Study 1: WIA

Ejection intraventricular differences became negative during end-ejection, reaching its minimal value during early isovolumic relaxation (5±11 ms after end-ejection

[median±interquartile range]). WIA demonstrated that peak REIVPD was only 25 ± 10 ms (median±interquartile range) before peak $dIw-/dt$ (Figure 1). The total energy of the flow expansion wave ($Iw-_{relax}$) very closely correlated with τ following an inverse exponential relationship ($R_{rm}=-0.93$; Figure 2A) and with the peak REIVPD following a direct linear relationship ($R_{rm}=0.89$; Figure 2B).

Experimental Study 2: Lusotropic Sensitivity

A wide range of lusotropic states was achieved, and interventions induced parallel changes in τ and REIVPDs (Table 1). The relationship between τ and peak REIVPD within animals ($R_{rm}=-0.80$; Figure 3) was better than with other noninvasive methods such as FPV, e$'_{septal}$, and e$'_{lateral}$ ($R_{rm}=0.63$, 0.07, and 0.71, respectively).

Experimental Study 3: Load Dependence

Analysis of absolute values and relative changes showed that REIVPD remained stable up to intensive values of preload reduction (Table 2). In fact, flow dependence of REIVPD was lower than of invasive τ and $(dP/dt)_{min}$ (Table 2).

Clinical Study

Clinical and hemodynamic data of the 50 patients are shown in Table 3. Correlation values of τ with $\tau_{nonzero}$ and τ_{logist} were 0.69 and 0.76, respectively ($P<0.05$ for both), whereas correlation between the latter 2 was 0.91 ($P<0.05$). Applicability and reproducibility of these indices of relaxation is shown in Table 4.

No correlation was found between τ and FPV (Figure 4A). Moderate correlations were observed between τ and e$'$ ($R=0.70$, Figure 4B) and REVIPD (0.71, Figure 4C). Bivariate regression showed that both e$'$ and REIVPD were independently related to τ (e$'$ $\beta_{std}=-0.48$; REIVPD $\beta_{std}=-0.50$; $P<0.0001$ for both), and no R^2 was lost when e$'$ and REIVPD were merged as a single product variable (adjusted $R^2=0.68$ versus 0.71, for bivariate and univariate fittings, respectively; Figure 4D). R_{boot} value for the τ versus e$'$ · REIVPD correlation was 0.84, significantly higher than values obtained for e$'$ (0.70) and REIVPD (0.71) separately ($P<0.05$ for both). The area under the ROC curve for predicting prolonged LV relaxation ($\tau \geq 50$ ms) for e$'$ · REIVPD was 0.96 (95% confidence interval, 0.85 to 0.99), with the best cutoff value of 25 cm·mm Hg/s (sensitivity, 86% [95% confidence interval, 57 to 98]; specificity, 93%[78–99]). Ejection fraction independently influenced the τ versus e$'$ relationship ($P=0.03$), whereas it had no effect neither on the τ versus REIVPD ($P=0.4$) nor on the τ versus e$'$ · REIVPD ($P=0.7$) relationships. The combined variable showed closer correlation with τ than e$'$, both in patients with normal (ejection fraction $>50\%$; $R_{boot}=0.84$ versus 0.64, $P<0.05$) and abnormal ($R_{boot}=0.78$ versus 0.54, $P<0.05$) ejection fraction. Correlations of noninvasive methods with alternative invasive τ indices are summarized in Table 4.

All noninvasive methods correlated moderately with pre-A LV pressure, showing R values of 0.43, 0.54, 0.60, and 0.57 for E/e$'$, E/FPV, E/REIVPD, and E/(e$'$ · REIVPD) ratios, respectively. Remarkably, these values were very close to the

R value of the correlation between pre-A LV pressure and the combination of E-wave velocity and invasive τ (E·τ $R=0.56$).

Discussion

The present study introduces a new color Doppler–based method to estimate the rate of LV relaxation noninvasively in clinical practice. Three sets of animal studies were used to prove the physiological basis of the method and demonstrated favorable reliability under a wide range of hemodynamic interventions. A simultaneous catheterization echo Doppler study in a heterogeneous patient group showed that the new method, combined with tissue Doppler mitral velocity, outperforms currently available methods to estimate the rate of relaxation. We believe our results are strengthened by important aspects aimed to control confusion factors: (1) a split within-subject (animal) and between-subject (clinical) analysis, (2) a specific load-dependence assessment, (3) simultaneous recording of invasive and noninvasive data and by same-beat analysis, both in animals and patients, and (4) statistical techniques to avoid overfitting in the clinical sample. To our knowledge, this is the first echo Doppler validation study that takes into account these methodological issues.

WIA of Early Diastole and LV Regional Pressure Gradients

During systole, a considerable amount of potential energy is stored by the LV. Intracellularly, recoil forces are generated when the large springlike protein titin is compressed beyond its equilibrium length. Myocardial relaxation is initiated by the intracellular calcium transient,[16] and the release of potential energy starts when actin-miosin bridges begin to deactivate. At the chamber integration level, the recoil effect is amplified by the 3-dimensional arrangement of myocardial fibers and is responsible for conformational and geometric changes of the LV chamber. The consequence is the generation of an expansion wave, which propagates from the LV apex toward the aorta, decreasing the pressure and velocity of ejection flow.

While this relaxation wave is building, reciprocal interactions among chamber and myocardium properties take place. Interdependent changes can be measured simultaneously in early diastolic myocardial wall strain,[17] conformational untwisting,[18] ejection flow deceleration, relaxation (the global value of τ, but also its regional isotropy and synchronicity),[19] and the development of regional pressure gradient fields.[20] We believe that the close correlation between $Iw-_{relax}$ and τ,[6] confirmed in our study, supports the role of $Iw-$ as a suitable index of overall early diastolic energy expenditure that comprehensively integrates these interdependent phenomena.

By definition, the expansion wave traveling from the LV to the aorta decreases ejection flow pressure and velocity. However, flow deceleration is inherently matched to the generation of a reversed (proximal$>$distal) pressure gradient, as formulated by the Euler momentum equation. Therefore, our observation of a close correlation between $Iw-_{relax}$ and REIVPD confirms this theoretical relationship and clarifies why the latter is an isovolumic index physiologically related to τ.

Table 2.   Hemodynamic Data During Preload Reduction by Caval Occlusion for Experimental Study 3

	Relative Change EDV, %			
	Preocclusion	0–5	5–10	10–15
Beats, n	24	42	40	21
LV end-diastolic volume, mL	63 (60 to 67)	62 (59 to 65)	59 (55 to 62)*	55 (52 to 58)*
LV end-diastolic pressure, mm Hg	15 (14 to 16)	11 (9 to 12)*	7 (6 to 8)*	5 (4 to 6)*
$(dP/dt)_{min}$, mm Hg/s	−1598 (−1787 to −1409)	−1536 (−1722 to −1351)*	−1465 (−1650 to −1280)*	−1344 (−1535 to −1153)*
τ, ms	53 (49 to 58)	52 (47 to 56)	51 (46 to 55)	50 (46 to 54)
Peak REIVPD, mm Hg	1.8 (1.4 to 2.2)	1.8 (1.4 to 2.2)	1.7 (1.2 to 2.1)	1.9 (1.5 to 2.3)
Relative change $(dP/dt)_{min}$, %	. . .	1 (−4 to 5)	−3 (−8 to 1)	−12 (−17 to −7)*
Relative change τ, %	. . .	−2 (−6 to 1)	−4 (−8 to 0)	−5 (−10 to −1)
Relative change REIVPD, %	. . .	−3 (−18 to 12)	3 (−12 to 19)	−9 (−26 to 8)

*$P<0.05$ versus preocclusion.

Data from 5 closed-chest animals. Values are presented as fixed effects (95% confidence intervals).

REIVPD for the Noninvasive Estimation of τ

Classic measurements derived from pulsed-wave Doppler of mitral inflow are conditioned by loading conditions[21] and show a very poor correlation with reference invasive parameters of LV diastolic function.[22] For this reason, mitral annulus velocity during the early filling phase obtained by DTI (e′ velocity)[23] and FPV[24] have been proposed as load-independent indices of LV relaxation, and its routine usage is recommended in current practice guidelines.[2] However, these indices are known to depend on preload[25–29] and are influenced by systolic function.[30,31] Correlation values of e′ velocity with τ as low as $R=0.30$ have been demonstrated in patients with normal systolic function.[32,33] Factors known to affect the value of e′ velocity are mitral valve disease, annular calcification, regional wall motion abnormalities, or conduction disturbances, among others. It is recognized that the clinical value of e′ to assess relaxation in a given patient is limited.[5] Our study, showing only moderate correlation during simultaneous acquisitions, corroborates this finding.

Peak REIVPD is reached during the isovolumic relaxation period, just after aortic valve closure, therefore justifying relative flow stability. Indices based on global LV flow dynamics account for global chamber performance, instead of local myocardial deformation or lengthening parameters. Therefore, regional wall motion or local structural abnormalities should only modify this index when the global chamber relaxation rate is affected. On a similar basis, we have previously demonstrated that intraventricular pressure differences provide useful surrogates of other chamber indices such as peak systolic elastance[8] and diastolic suction.[34]

Recent animal studies have demonstrated that e′ is conditioned by restoring forces and lengthening load, in addition to LV relaxation.[35] LV restoring forces are responsible for diastolic suction during early filling and are a mechanism related to REIVPD during late ejection, as suggested by our WIA analysis. Because these factors are very closely related, probably, correcting for this effect explains the advantage of e′·REVIPD over e′ to estimate τ in a wide group of patients with normal and abnormal systolic function. Remarkably, the e′·REVIPD product also improved noninvasive estimation of

$\tau_{nonzero}$ and τ_{logist}, currently proposed as more robust indices of global chamber relaxation than τ.[13]

Limitations for Estimating LV Filling Pressures

All methods tested were suboptimal to estimate LV filling pressure, in agreement with recent studies in patients with normal[3] and abnormal[36] systolic LV function. The rationale for using noninvasive relaxation surrogates to estimating filling pressures is based on the assumption that E-wave velocity is determined by left atrial pressure and the rate of relaxation.[37] However, the fact that E-wave velocity corrected by measured invasive τ did not perform better suggests that E-wave velocity is probably influenced by additional variables beyond atrial pressure and τ. In this context, the role of diastolic suction and intraventricular vorticity deserves further exploration. Additionally, whether passive diastolic properties can also be derived from intraventricular flow dynamic parameters should be investigated.

Study Limitations

The 3-dimensional nature of intraventricular flows is a well-known limitation of the CDMM approach to measure pressure gradients and has been extensively addressed and discussed elsewhere.[8] Although limitations of applying a 1-dimensional WIA to study LV filling are recognized,[6] we believe that they do not invalidate the results of our study. Because simultaneous velocity locations were not recorded at the LV inflow and outflow, WIA was not extended to the early filling period, and the $Iw-$ component related to mitral filling was not measured. However, this contribution to total aspirating energy is <10% and constant over different lusotropic states. Thus, we believe that $Iw-_{relax}$ is a suitable index for the WIA performed in our study. The fact that echocardiographic studies were performed during simultaneous catheterization may be a limitation for image quality. However, 74% of clinical studies were performed in the left lateral decubitus using a radial approach, and we believe this a slight reduction in image quality is outweighed by abolishing the source of variability due to changing adrenergic tone and hemodynamic conditions when studies are performed in different scenarios.

Table 2. Continued

15–20	20–25	25–30	30–35	35–40	P
21	21	20	19	16	
52 (49 to 55)*	49 (46 to 52)*	46 (43 to 49)*	42 (39 to 46)*	38 (35 to 42)*	<0.001
3 (2 to 5)*	3 (2 to 4)*	2 (1 to 4)*	1 (0 to 3)*	1 (−1 to 2)*	<0.001
−1269 (−1460 to −1078)*	−1158 (−1349 to −967)*	−1065 (−1257 to −873)*	−1030 (−1223 to −837)*	−1054 (−1250 to −858)*	<0.001
50 (46 to 55)	50 (46 to 55)	49 (45 to 54)*	50 (46 to 55)	48 (43 to 53)*	0.01
1.8 (1.4 to 2.2)	1.8 (1.3 to 2.2)	1.7 (1.2 to 2.1)	1.6 (1.2 to 2.0)	1.4 (0.9 to 1.8)*	0.02
−19 (−24 to −14)*	−26 (−31 to −20)*	−31 (−36 to −25)*	−35 (−40 to −30)*	−34 (−39 to −28)*	<0.001
−4 (−9 to 0)	−5 (−9 to 0)	−7 (−11 to −2)*	−5 (−10 to −1)	−7 (−12 to −2)*	0.07
−5 (−21 to 12)	−5 (−22 to 12)	−4 (−21 to 13)	−3 (−21 to 14)	7 (−11 to 26)	0.55

Potential Clinical Applications

Animal experiments demonstrated relative flow stability of REIVPDs. In clinical terms, this translated into an improved estimation of relaxation both in patients with normal systolic function and those with abnormal systolic function. Correlation with τ for the $e' \cdot$ REIVPD index was 31% and 45% higher than for e'. Because relaxation is usually impaired in patients with abnormal systolic function, a more reliable

Table 3. Demographic, Catheterization, and Doppler Echocardiography Data for the Clinical Study

	Total	Ejection Fraction <50%	Ejection Fraction ≥50%	P
n	50	27	23	
Age, y	58±13	59±11	57±15	0.6
Sex, male/female	37/13	21/6	16/7	0.5
Heart rate	72±13	77±12	65±13	0.004
QRS >120 ms	21	15	6	0.03
Invasive				
Peak LV pressure, mm Hg	131±31	126±30	136±33	0.3
Pre-A LV filling pressure, mm Hg	13±6	14±6	11±5	0.04
$(dP/dt)_{min}$, mm Hg/s	−1495±427	−1249±353	−1783±312	<0.001
τ, ms	57±12	61±11	52±11	0.006
$\tau_{nonzero}$, ms	94±32	102±32	86±32	0.001
$\tau_{logistic}$, ms	38±16	44±17	32±12	0.008
Doppler echocardiography				
End-diastolic volume, mL	109±43	130±44	85±26	<0.001
End-systolic volume, mL	65±43	93±41	34±15	<0.001
Ejection fraction	0.45±0.19	0.31±0.10	0.63±0.08	<0.001
LV mass, g/m²	94±32	102±32	86±32	0.1
Mitral regurgitation class III or IV/IV	9	5	4	0.9
Isovolumetric relaxation time, ms	100±33	96±39	104±27	0.4
E, cm/s	66±23	65±28	67±16	0.7
Deceleration time, ms	169±68	148±69	190±62	0.04
E/A	1.0±0.5	1.1±0.7	0.9±0.3	0.26
e' septal, cm/s	6±3	5±2	7±3	0.02
e' lateral, cm/s	9±3	8±3	10±3	0.03
e' average, cm/s	8±3	7±3	8±3	0.02
E/e'	10±5	11±7	8±2	0.07
Flow propagation velocity, cm/s	49±14	46±14	52±12	0.13
REIVPD, mm Hg	2.8±1.5	2.2±1.0	3.6±1.6	0.002
log($e'\cdot$REIVPD), cm·mm Hg/s	2.9±0.7	2.6±0.6	3.3±0.7	<0.001

Values are expressed as mean±SD.

Table 4. Applicability and Reproducibility Data for Invasive Methods of Estimating Relaxation in the Clinical Study and Correlation With Noninvasive Methods

	τ	$\tau_{nonzero}$	$\tau_{logistic}$
Applicability and reproducibility			
Patients without convergence of fitting algorithm, n (%)	0 (0%)	3 (6%)	1 (2%)
Absolute beat-to-beat variability, ms (R_{ic})	2±3 (0.98)	1±13 (0.97)	2±8 (0.87)
Relative beat-to-beat variability, %	3±5%	1±13%	5±25%
Correlation with noninvasive indices			
E', R	0.70*	0.52*	0.54*
log(REIVPD), R	0.71*	0.59*	0.67*
log(e' · REIVPD), R	0.84*	0.67*	0.74*

R_{ic} indicates intraclass correlation coefficient; R, Pearson correlation coefficient.
*$P<0.05$.

index for patients with this condition could be particularly useful in the clinical setting. Other specific scenarios where the e' · REIVPD index would be preferred are those in which the e' velocity is known to be unreliable. Typical situations are patients with regional wall motion abnormalities, conduction disturbances, or mitral valve disease. In the future,

integration into the scanner software, as well as semiautomatic CDMM image processing[38] and 2D extensions of the method,[39] are promising technological developments that could facilitate widespread generalization of noninvasive measurements of intracardiac flow dynamics in clinical practice.

Conclusions

Doppler-derived measurements of REIVPDs provide a sensitive, reliable, reproducible, and relatively load-independent index of the rate of LV relaxation. When combined with early myocardial lengthening velocity, this method improves the assessment of LV relaxation in the clinical setting.

Clinical Summary

Recent studies have shown the limitations of Doppler-derived methods to evaluate ventricular relaxation in the clinical setting. In the present study, we propose and validate a new noninvasive index that improves the assessment of LV relaxation in patients. At end-systole, myocardial relaxation causes flow deceleration and a reversed pressure gradient inside the LV that can be measured using Doppler echocardiography. In an animal model, we demonstrate, for the first time, the physiological basis of the Doppler-derived peak REIVPD to assess relaxation and its reliability under a wide range of hemodynamic interventions and loading conditions. A clinical validation study in 50 patients undergoing simul-
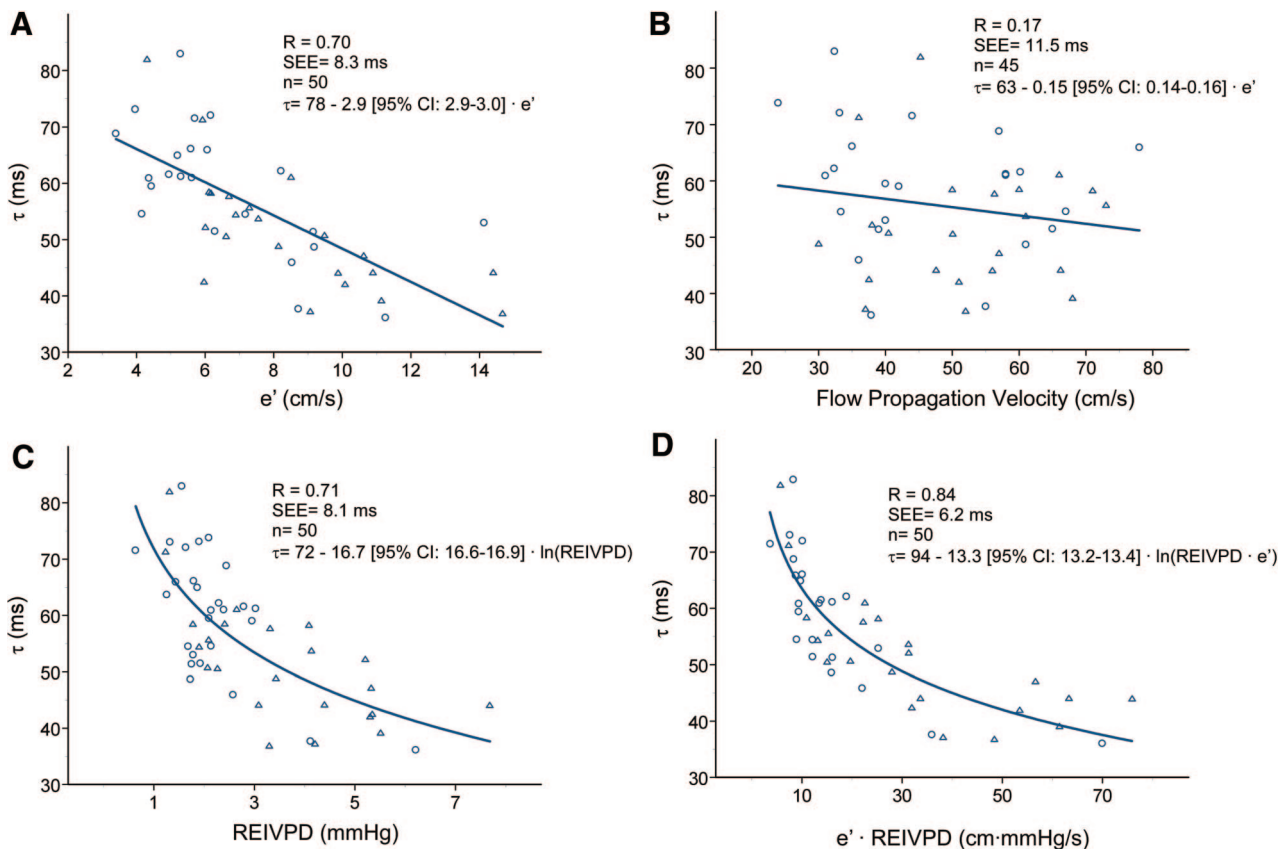

Figure 4. Results of the clinical validation study. A, Correlation between τ and flow propagation velocity (FPV). B, Correlation between τ and mitral annulus e' wave-lengthening velocity. C, Correlation between τ and REIVPD. D, Correlation between τ and the product variable e' · REIVPD. Δ indicates ejection fraction ≥ 0.5; $\bigcirc$, ejection fraction <0.5; and SEE, standard error of the estimate.

taneous Doppler echocardiography and high-fidelity LV pressure measurements shows that the new method combined with tissue Doppler mitral-annulus velocity (e′) outperforms currently available methods to estimate the rate of relaxation. This new method might be preferred in clinical scenarios where e′ is known to be unreliable, such as mitral valve disease, annular calcification, regional wall motion abnormalities, or conduction disturbances.

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Disclosures

None.

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CLINICAL PERSPECTIVE

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