Clinical value of echocardiographic Doppler-derived right ventricular d*p*/d*t* in patients with pulmonary arterial hypertension

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Aims	Right ventricular (RV) d*p*/d*t* is the instantaneous rate of RV pressure rise during early systole and is a surrogate marker of RV contractility. The main objective of this study was to evaluate the ability of echocardiographic Doppler obtained RV d*p*/d*t* to predict long-term survival in patients with pulmonary arterial hypertension (PAH) and chronic thrombo-embolic pulmonary hypertension (CTEPH).
Methods and results	Seventy-eight consecutive newly diagnosed untreated patients (64 ± 15 years, 71% female, 57% PAH, 43% inoperable CTEPH) were included in the study. At baseline, patients were assessed clinically [New York Heart Association (NYHA) and 6 minutes walking distance (6MWD)], by transthoracic cardiac ultrasound and by right heart catherization. RV d*p*/d*t* was assessed using spectral Doppler recordings from the tricuspid regurgitation signal at a sweep speed of 200 mm/s by measuring the time interval in which the regurgitant velocity increased from 0.5 to 2 m/s. During a mean follow-up period of 3.5 ± 1.7 years, 31 patients died and 3 received a lung transplant [study endpoint reached in 34/78 (44%) patients]. The optimal RV d*p*/d*t* cut-off was determined by receiver operating characteristic analysis at 3 years to be 410 mmHg/s (specificity 84%, positive-predictive value 55%, and negative-predictive value 83%). In univariate analysis, RV d*p*/d*t* <410 mmHg/s (hazard ratio 2.67, 95% CI 1.30−5.47, *P* = 0.007), tricuspid annulus plane systolic excursion (TAPSE) <15 mm, NYHA, 6MWD, and right atrial pressure were predictors of mortality. In a multivariate model with TAPSE, RV d*p*/d*t* remained an independent predictor of mortality (*P* = 0.01).
Conclusion	A reduced baseline RV d*p*/d*t* is a clear indicator of poor outcome independent of TAPSE in patients with PAH/CTEPH.
Keywords	Right ventricular function • Pulmonary hypertension

Introduction

Adequate assessment of right ventricular (RV) function is an essential component of risk stratification in patients with pulmonary hypertension (PH) since two-thirds of total mortality may be attributed to RV failure.[1,2] The complex 3D shape of the RV and poor endocardial definition greatly complicate volumetric RV function techniques by 2D echocardiography.[3] The ideal RV function parameter should predict long-term clinical outcome, be easy to obtain, reproducible, and parallel functional capacity. Current guidelines recommend the use of a combination of clinical [New York Heart Association class

(NYHA) and 6 minutes walking distance (6MWD)], invasive [right atrial pressure (RAP) and cardiac index (CI)], and echocardiographic parameters for risk stratification in PH patients. Many echocardiographic parameters are related to prognosis in PH.[4−11] However, awaiting further validation studies, only TAPSE and the presence of pericardial fluid are recommended in the guidelines as prognostic parameters in PH.[12]

RV d*p*/d*t* is the instantaneous rate of RV pressure rise during early systole and is a surrogate marker of RV contractility. RV d*p*/d*t* can easily be obtained by continuous-wave Doppler of the tricuspid regurgitation (TR) jet and measuring the time interval necessary for

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the RV to build up a predefined pressure difference. Non-invasive Doppler obtained RV peak positive dp/dt showed a good correlation with right heart catheterization (RHC)-derived dp/dt, irrespective of the level of RAP.[13,14] There are no data on the value of RV dp/dt as a predictor of long-term clinical outcome. Therefore, we performed this validation study to evaluate (i) the ability of RV dp/dt to predict long-term survival in patients with pulmonary arterial hypertension (PAH) and chronic thrombo-embolic pulmonary hypertension (CTEPH), (ii) its correlation with functional capacity, and (iii) interobserver variability.

Methods

Study design

All patients with PH referred to our tertiary care hospital are consecutively included in the 'UZ Leuven PH database'. For this study, we selected all newly diagnosed and so far untreated adult patients referred between 2006 and 2009 with PAH or inoperable CTEPH.[15] Baseline assessment includes clinical parameters (NYHA and 6MWD if feasible), echocardiography, and RHC. Eight patients were excluded because of an inappropriate TR signal. The final study population consisted of 78 patients. All patients received appropriate state-of-the-art treatment including phosphodiesterase-5 inhibitors, endotheline receptor antagonists, prostacyclin analogues, or atrial septostomy. Primary endpoint was all-cause mortality. Three patients with irredeemable deterioration received a lung transplant and were assimilated to death. Survival time was estimated as the time from baseline echocardiography to the end of the study (31 December 2012) or death/transplantation. At study termination, the vital status was checked by review of the medical records or by phone contact. A minimal follow-up period was 3 years. The follow-up rate was 100%. The ethics committee of UZ Leuven approved the protocol. Because the protocol was judged to pose a low risk, the obligation for a written informed consent was waived.

Echocardiography

Baseline echocardiographies were performed on a Vivid 7 or Vivid E9 ultrasound system (GE Vingmed Ultrasound, Horten, Norway) as well as Philips iE 33 (Royal Philips Electronics, Eindhoven, Netherlands). Baseline recordings were retrospectively re-analysed using a clinical postprocessing workstation (EchoPAC, GE Vingmed Ultrasound) by two completely blinded cardiologists (Ameloot Koen and Palmers Pieter-Jan). Both were not involved in routine assessment of study patients and were unaware of the clinical course of patients during follow-up. RV dp/dt was assessed using spectral Doppler recordings from the TR signal at a sweep speed of 200 mm/s by measuring the time interval in which the regurgitant velocity increased from 0.5 to 2 m/s (1–16 mmHg) (*Figure 1*). These velocities were chosen as being most robust for reading while resulting in the best correlation with invasive measurements.[13] In patients with sinus rhythm, three random beats were averaged to obtain the final RV dp/dt value. In six patients with atrial fibrillation, five beats were averaged. Furthermore, a complete 2D, Doppler, and M-mode examination was performed as recommended in guidelines for the assessment of PH patients.[12,16]

Haemodynamics

In 49 patients, routine RHC with the measurement of pulmonary pressures, mixed venous oxygen saturation, and assessment of CI by thermodilution and Fick's principle was performed within 10 days of baseline echocardiography. In 21 patients, RHC was performed with a larger time interval (median 26 days). Their data were not used for correlation

with echocardiographic data. One PAH patient refused RHC. In seven CTEPH patients, with mild PH and preserved functionality (NYHA I) or with advanced age or co-morbidity, no RHC was performed. None of these patients had echocardiographic evidence of left-sided diastolic dysfunction.

Data analysis

Continuous variables were summarized as mean ± SD or as median with interquartile range as appropriate, and categorical variables as the number of subjects and percentage. A predictive model for all-cause mortality was constructed. First, a receiver operating characteristic (ROC) curve was constructed to test the ability of RV dp/dt to predict mortality within 3 years after baseline echocardiography. Secondly, uni- and multivariate Cox proportional hazards regression models were used to describe the prognostic properties of RV dp/dt in relationship with the other clinical, haemodynamic, and echocardiographic parameters. A two-step multivariate model was used: first, RV dp/dt was adjusted for TAPSE to construct a model with only echocardiographic predictors. Secondly, the combination of these echocardiographic predictors was adjusted for clinical parameters (NYHA and 6MWD) to construct a model with only non-invasive parameters. Thirdly, survival curves using the Kaplan–Meier method were constructed and compared by the log-rank test. Finally, baseline and 'final' RV dp/dt were compared by a paired-sample Wilcoxon signed-rank test in patients who died during follow-up if a final echo was available <6 months before death. Patients surviving <6 months were excluded from this analysis. Subgroups with preserved and reduced RV dp/dt were compared by unpaired Student's *t*-tests. To assess the relation between RV dp/dt and functional capacity, ANOVA was used to compare the proportion of patients with preserved RV dp/dt per NYHA class and linear regression to describe correlation with 6MWD. Interobserver variability was assessed by linear regression, Pearson correlation coefficients, Bland–Altman plot, and by the percentage interobserver variability (absolute difference between two observations divided by the means and expressed as percentage). Data by both observers were compared using paired-sample Student's *t*-test. The level of concordance was calculated as the proportion of patients classified similarly by both observers (either preserved or reduced RV dp/dt). Statistical analysis was performed using the Matlab software (version R2010b, Mathworks, USA). A *P*-value of <0.05 was considered significant.

Results

Study population

Baseline parameters illustrate the disease severity of the study cohort (*Table 1*). During a mean follow-up period of 3.5 ± 1.7 years (minimal 3.0–maximal 6.7 years), 31 patients died (mean after 2.3 ± 1.6 years) and 3 received a lung transplant. The study endpoint was reached in 34/78 (44%) of the patients. The vast majority of the study patients died due to a combination of respiratory insufficiency and right-sided heart failure with refractory fluid overload or arrhythmias.

Survival analysis

A ROC curve on the ability to predict all-cause mortality within 3 years after echocardiography identified the optimal cut-off for RV dp/dt to be 410 mmHg/s (specificity 84%, positive-predictive value 55%, and negative-predictive value 83%) (*Figure 2*). Efficiency (the proportion of patients correctly classified) was 76%. RV dp/dt, TAPSE, 6MWD, and NT-proBNP showed good and equivalent
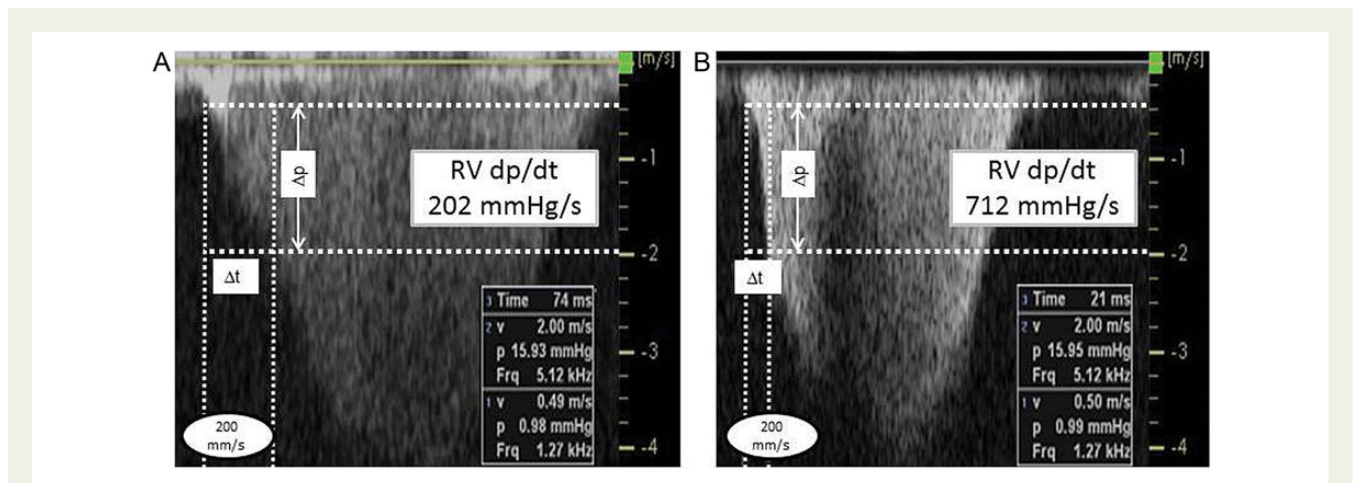
Figure 1: Determination of RV dp/dt: RV dp/dt was assessed using continuous-wave Doppler recordings from the TR signal at a sweep speed of 200 mm/s. The time interval (Δt) in which the regurgitant velocity increased from 0.5 to 2 m/s (1–16 mmHg, $\Delta P = 15$ mmHg) was measured. RV dp/dt equals ΔP divided by Δt. (A) A 79-year-old female patient with systemic sclerosis. RV dp/dt was reduced (202 mmHg/s). RHC revealed an mPAP of 41 mmHg, CI 2.6 l/min/m^2, and RAP 13 mmHg. This patient died 9 months after baseline ultrasound. (B) A 62-year-old female patient with PAH. RV dp/dt was preserved (712 mmHg/s). RHC revealed an mPAP of 52 mmHg, CI 2.3 l/min/m^2, and RAP 3 mmHg. This patient is still alive after 6.2 years. RHC, right heart catherization; mPAP, mean pulmonary arterial pressure; CI, cardiax index; RAP, right atrial pressure.

accuracy. None of these parameters was superior to another (all one-tailed P-values, NS). Tei index, RAP, and CI by thermodilution were not predictive at this time point (Table 2).

RV dp/dt was reduced in 13/34 (38%) of the patients that reached the primary study endpoint (mean 280 ± 81 mmHg/s). In the remaining 21/34 (62%) patients, RV dp/dt was preserved (mean 844 ± 356 mmHg/s). RV dp/dt was reduced in 8/44 survivors (mean 267 ± 85 mmHg/s). In the remaining 36/44 survivors, RV dp/dt was preserved (mean 770 ± 326 mmHg/s).

Significant univariate predictors of all-cause mortality by Cox regression included baseline RV dp/dt <410 mmHg/s, NYHA, 6MWD, RAP, and TAPSE <15 mm (Table 3). Indexation of RV dp/dt by afterload (systolic pulmonary arterial pressure) or preload (right ventricular end-diastolic area, RVEDA) did not improve the prognostic properties of RV dp/dt alone. In a first multivariate model, RV dp/dt remained an independent predictor of mortality when combined with TAPSE <15 mm. The combination of either a reduced TAPSE or RV dp/dt was an independent predictor of mortality when adjusted for NYHA and 6MWD (Table 4).

Kaplan–Meier survival curves are shown in Figure 3. The estimated median survival time of patients with reduced RV dp/dt (3.13 years, 95% CI 2.03–4.23) was significantly lower compared with those with preserved RV dp/dt (5.03 years, 95% CI 4.44–5.62) (log-rank χ^2 7.81, $P = 0.005$). The estimated median survival time of patients with both reduced RV dp/dt and reduced TAPSE (2.37 years, 95% CI 1.01–3.73) was significantly lower compared with those with only one poor survival predictor (3.92 years, 95% CI 3.08–4.75) or both preserved TAPSE and RV dp/dt (5.68 years, 95% CI 5.03–6.32) (log-rank χ^2 15.39, $P < 0.0001$).

In 12 patients, a final RV dp/dt value could be determined <6 months before death. Compared with baseline values, final RV dp/dt was significantly reduced [median 529 (251–653) vs. 206 (125–327) mmHg/s, $P = 0.0001$; Figure 4].

Preserved vs. reduced RV dp/dt

The RV was significantly more dilated in patients with reduced RV dp/dt. Levels of NT-proBNP, RHC pressures, CI, and TAPSE were not significantly different between the cohorts with preserved and reduced RV dp/dt (Table 1). When patients were stratified according to their grade of TR, RV dp/dt was not significantly different in patients with light-to-moderate TR compared with severe TR (611 ± 371 vs. 719 ± 366 mmHg/s, $P = 0.20$).

Functional capacity

A reduced baseline RV dp/dt was associated with a higher NYHA class and lower 6MWD (Table 1). The proportion of patients with a preserved RV dp/dt was significantly lower with an increasing NYHA class (Figure 5). Linear regression revealed a weak significant correlation between RV dp/dt and 6MWD ($R = 0.28$, $P = 0.02$).

Interobserver variability

The level of concordance between observers regarding the distinction of 'preserved' and 'reduced' RV dp/dt was high (92.3%). Interobserver variability was 9.9%. Pearson correlation coefficient was 0.63, with a mean bias 59.9 mmHg/s. The Bland–Altman plot revealed that most of this variability was attributable to measurement variation in patients with a high (i.e. preserved) RV dp/dt. A paired-sample t-test did not show significant differences between datasets by both observers ($P = 0.10$; Figure 6).

Discussion

Survival analysis

The current study shows for the first time that a reduced baseline RV dp/dt as a surrogate marker for reduced RV contractility is a clear indicator of poor prognosis in patients with PAH/CTEPH. A previous

Table 1 Baseline demographics, diagnosis, clinical characteristics, haemodynamic and echocardiographic parameters of the overall cohort and stratified by normal or reduced RV dp/dt

	All patients	RV dp/dt (mmHg/s)		
		<410	≥410	*P*-value
Demographics				
Number of patients	78	21	57	
Age (years)	63.6 ± 15.2	69.8 ± 14.7	61.4 ± 14.9	0.03
Gender (female), *n* (%)	55 (70%)	12 (57%)	43 (75%)	0.15
Cause pulmonary hypertension, *n* (%)				
CTEPH	34 (43%)	8 (38%)	26 (46%)	/
PAH	44 (56%)	13 (62%)	31 (54%)	/
Clinical characteristics [*n* = 78 (NYHA), *n* = 68 (6MWD), *n* = 49 (NT-proBNP)]				
NYHA	2.8 ± 0.7	3.1 ± 0.6	2.7 ± 0.7	0.001
6MWD (m)	309 ± 160	259 ± 122	356 ± 149	0.003
NT-proBNP (ng/L)	2059 (635; 4439)	3085 (695; 6217)	1877 (630; 3450)	0.18
Right heart haemodynamics (*n* = 70, 49 patients within 10 days of echo)				
Heart rate (bpm)	77.7 ± 16.0	75.6 ± 13.3	80.3 ± 16.0	0.10
RAP (mmHg)	5 (3; 9)	4 (3; 13)	5 (2.2; 10.7)	0.21
sPAP (mmHg)	77.6 ± 20.0	83.3 ± 21.3	75.9 ± 21.4	0.14
dPAP (mmHg)	29.4 ± 10.6	34.2 ± 13.7	29.0 ± 10.1	0.10
mPAP (mmHg)	44.7 ± 11.8	48.9 ± 11.4	43.5 ± 12.7	0.08
PAOP (mmHg)	8.1 ± 3.9	8.9 ± 4.4	7.9 ± 4.1	0.23
CI (L/min/m^2)	2.0 ± 0.5	2.0 ± 0.5	2.0 ± 0.6	0.40
SVI (mL/m^2)	28.0 ± 9.4	24.5 ± 7.0	28.0 ± 9.4	0.08
SVO$_2$ (%)	62.3 ± 7.7	59.9 ± 5.5	63.1 ± 7.4	0.06
PVRI (dyne s cm^{-5})	891 ± 409	919 ± 424	914 ± 458	0.48
Echocardiographic parameters (*n* = 78)				
RVEDA (cm^2)	28.0 ± 7.9	31.3 ± 7.6	26.8 ± 7.7	0.01
RVEDA/LVEDA	1.5 ± 0.8	1.9 ± 1.0	1.3 ± 0.6	0.01
LVEF (%)	64.0 ± 7.1	63.4 ± 8.0	64.2 ± 6.8	0.34
Grade TR	2.7 ± 0.8	2.9 ± 0.8	2.6 ± 0.9	0.14
sPAP (mmHg)	70.8 ± 19.0	78.3 ± 18.7	68.1 ± 18.5	0.02
PAT (ms)	70.6 ± 20.3	61.5 ± 21.7	74.3 ± 18.8	0.01
RVET (ms)	297 ± 68	290 ± 56	300 ± 72	0.28
IVC collapsability, *n* (%)	50 (64%)	16 (76%)	34 (59%)	0.13
Pericardial fluid, *n* (%)	25 (32%)	9 (43%)	16 (29%)	0.13
TAPSE (mm)	17 ± 5	16 ± 5	17 ± 6	0.20
TEI	0.7 ± 0.3	0.8 ± 0.3	0.6 ± 0.3	0.01

CTEPH, chronic thrombo-embolic pulmonary hypertension; PAH, pulmonary arterial hypertension; NYHA, New York Heart Association; 6MWD, 6 minutes walking distance; RAP, right atrial pressure; sPAP, systolic pulmonary arterial pressure; dPAP, diastolic pulmonary arterial pressure; mPAP, mean pulmonary arterial pressure; PAOP, pulmonary arterial occlusion pressure; CI, cardiac index; SVI, stroke volume index; SVO$_2$, mixed venous oxygen saturation; PVRI, pulmonary vascular resistance index; RVEDA, right ventricular end-diastolic area; LVEDA, left ventricular end-diastolic area; LVEF, left ventricular ejection fraction; TR, tricuspid regurgitation; PAT, pulmonary acceleration time; RVET, right ventricular ejection time; IVC, inferior vena cava; TAPSE, tricuspid annulus plane systolic excursion.

study showed the mean echocardiographic RV dp/dt in healthy subjects to be 1016 mmHg/s.[17] This contrasts with our presented RV dp/dt cut-off (<410 mmHg/s) and with the mean RV dp/dt in our study cohort (658 ± 371 mmHg/s). A reduced baseline RV dp/dt was associated with a 2.57-fold increased risk of death and a 3-year survival rate of 45% compared with 83% in patients with a preserved baseline RV dp/dt. We also showed that RV dp/dt is a dynamical parameter that further decreases in patients short before death. The prognostic properties of RV dp/dt have not been evaluated before. Therefore,

routine determination of RV dp/dt is currently not recommended in the guidelines.[12,16] In contrast, TAPSE has been extensively validated in previous studies and is widely used as the most accurate echocardiographic tool for risk stratification in patients with PH- or non-PH-induced RV failure.[4–6,11] We demonstrated that RV dp/dt and TAPSE have equivalent accuracy in predicting long-term survival and are additive to each other. Three major physiological explanations for these findings apply. First, RV dp/dt reflects the complex interaction of all muscle fibres building up RV pressure during early
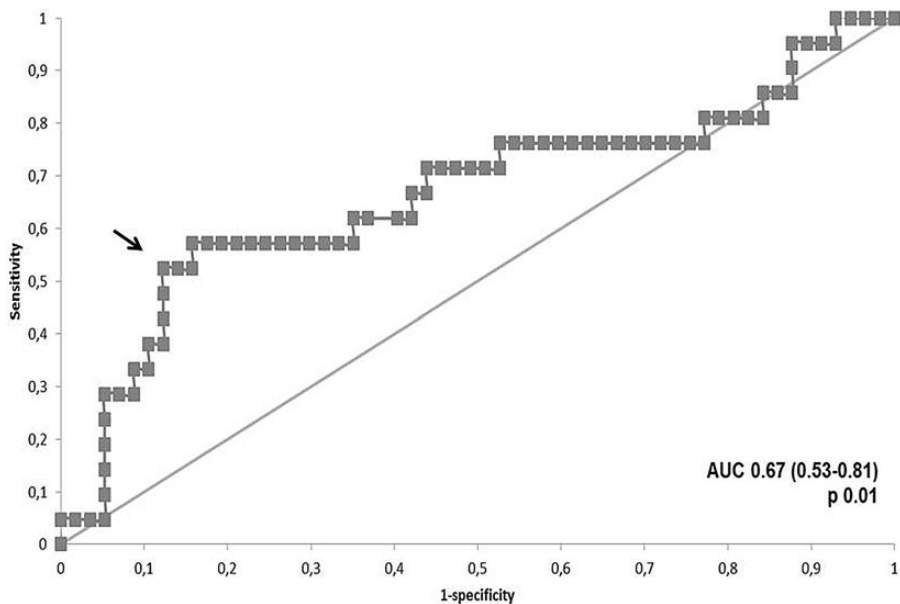
Figure 2: ROCs on the ability of RV d*p*/d*t* to predict all-cause mortality within 3 years after baseline echocardiography. The arrow indicates the optimal cut-off point (RV d*p*/d*t* 410 mmHg/s). AUC, area under curve.

Table 2 Area under the ROC curve, sensitivity, specificity, positive- and negative-predictive values, and efficiency for suggested cut-off points for RV d*p*/d*t* and other echocardiographic, clinical, biochemical, and RHC parameters to predict all-cause mortality within 3 years after baseline echocardiography

	RV d*p*/d*t*	TAPSE	Tei	6MWD	proBNP	RAP	CI
AUC	0.67	0.66	0.50	0.75	0.79	0.50	0.61
95% CI	0.53−0.81	0.51−0.80	0.36−0.65	0.60−0.89	0.64−0.96	0.35−0.65	0.46−0.76
P-value	0.01	0.01	NS	0.0003	0.0001	NS	NS
Optimal cut-off	<410 mmHg/s	<15 mm	>0.70	<200 m	>1400 ng/L	<10 mmHg	<2.0 L/min/m^2
Sensitivity	52.38	52.38	52.38	55.56	83.33	31.58	70.00
Specificity	84.21	75.00	44.64	86.00	75.68	88.00	55.10
PPV	55.00	44.00	26.19	58.82	52.63	50.00	38.89
NPV	82.76	80.77	71.43	84.31	93.33	77.19	81.82
Efficiency	75.64	68.83	46.75	77.94	77.55	72.46	59.42
PLR	3.32	2.10	0.95	3.97	3.32	2.58	1.56

TAPSE, tricuspid annulus plane systolic excursion; 6MWD, 6 minutes walking distance; BNP, brain natriuretic peptide; CI, cardiac index; AUC, area under curve; 95% CI, 95% confidence interval; PPV, positive-predictive value; NPV, negative-predictive value.

systole, whereas TAPSE predominantly reflects shortening of the longitudinal oriented muscle fibres primarily involved in ejection of blood.[3,18] Other surrogate parameters of isovolumetric contraction such as tissue Doppler obtained peak isovolumetric contraction velocity also showed to be a predictor of mortality in PH patients.[19] It may be hypothesized that a steeper rate of RV pressure rise during early systole results in an earlier pulmonary valve opening, thereby extending ejection time and increasing RV stroke volume.

Secondly, many patients with severe PH also have moderate or severe TR (57% in our study population). In patients with severe TR, TAPSE represents the combination of forward and backward flow and may be too optimistic as an estimator of true forward RV stroke volume. However, accuracy of RV d*p*/d*t* in these patients may also be questioned since severe TR results in faster RA−RV pressure equilibration. Moreover, the usually neglected inertia term of the complete Bernoulli equation may become relevant in severe TR. Thirdly, TAPSE can be falsely elevated in patients with a failing RV

Table 3 Univariate predictors of all-cause mortality by Cox regression

	HR	95% CI	P-value
Demographics			
Age per year	1.02	0.99–1.05	0.08
Female gender	1.50	0.74–3.06	0.26
Clinical characteristics			
NYHA	2.74	1.47–5.12	0.001
6MWD per 50 m	0.80	0.58–1.65	0.002
NT-proBNP >1400 ng/L	2.78	0.63–12.26	0.07
Right heart haemodynamics			
RAP per mmHg	1.03	1.00–1.05	0.02
sPAP per mmHg	1.01	0.99–1.03	0.13
CI ≤2.0 L/min/m^2	1.83	0.55–6.03	0.10
SVO$_2$ per %	0.99	0.94–1.05	0.84
PVRI per dyne s cm^{-5}	1.00	1.00–1.00	0.29
Echocardiographic parameters			
RV dp/dt <410 mmHg/s	2.67	1.30–5.47	0.007
RV dp/dt/sPAP <5.7/s	2.55	1.26–5.15	0.009
RV dp/dt/RVEDA <15 mmHg/s/cm^2	2.25	1.11–4.56	0.02
TAPSE <15 mm	2.70	1.33–5.49	0.006
Tei > 0.70	1.17	0.36–3.83	0.65
RVEDA per cm^2	1.02	0.76–1.36	0.39
RVEDA/LVEDA	1.35	0.90–2.01	0.15
Grade TR	1.53	0.96–2.44	0.08
sPAP per mmHg	1.00	0.99–1.02	0.41
Pericardial fluid	1.61	0.80–3.26	0.18

HR, hazard ratio; NYHA, New York Heart Association; 6MWD, 6 minutes walking distance; BNP, brain natriuretic peptide; RAP, right atrial pressure; sPAP, systolic pulmonary arterial pressure; CI, cardiac index; SVO$_2$, mixed venous oxygen saturation; PVRI, pulmonary vascular resistance index; TAPSE, tricuspid annulus plane systolic excursion; RVEDA, right ventricular end-diastolic area; LVEDA, left ventricular end-diastolic area; TR, tricuspid regurgitation.

Table 4 Multivariate cox regression (primary endpoint all-cause mortality)

	Adjusted HR	95% CI	P-value
RV dp/dt <410 mmHg/s	2.51	1.21–5.20	0.01
TAPSE <15 mm	2.53	1.25–5.15	0.01
≥1/2 clinical indicator (NYHA III–IV or 6MWD <200 m)	2.97	0.63–13.98	0.08
≥1/2 echo indicator (RV dp/dt <410 mmHg/s or TAPSE <15 mm)	2.46	0.71–8.60	0.02

TAPSE, tricuspid annulus plane systolic excursion; HR, hazard ratio; NYHA, New York Heart Association; 6MWD, 6 minutes walking distance.
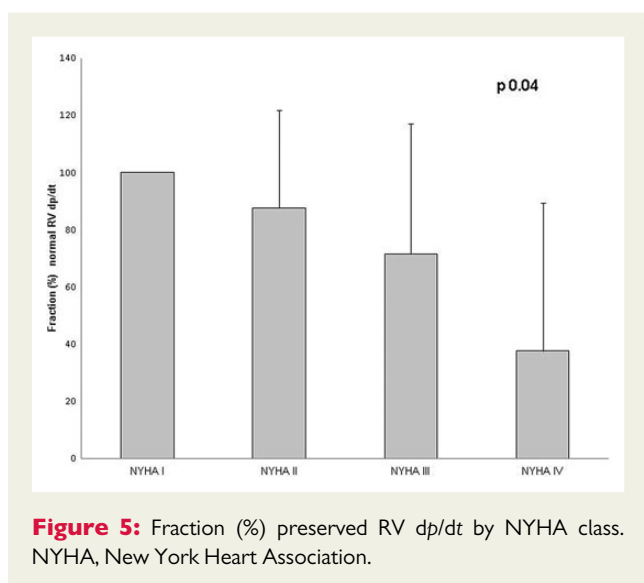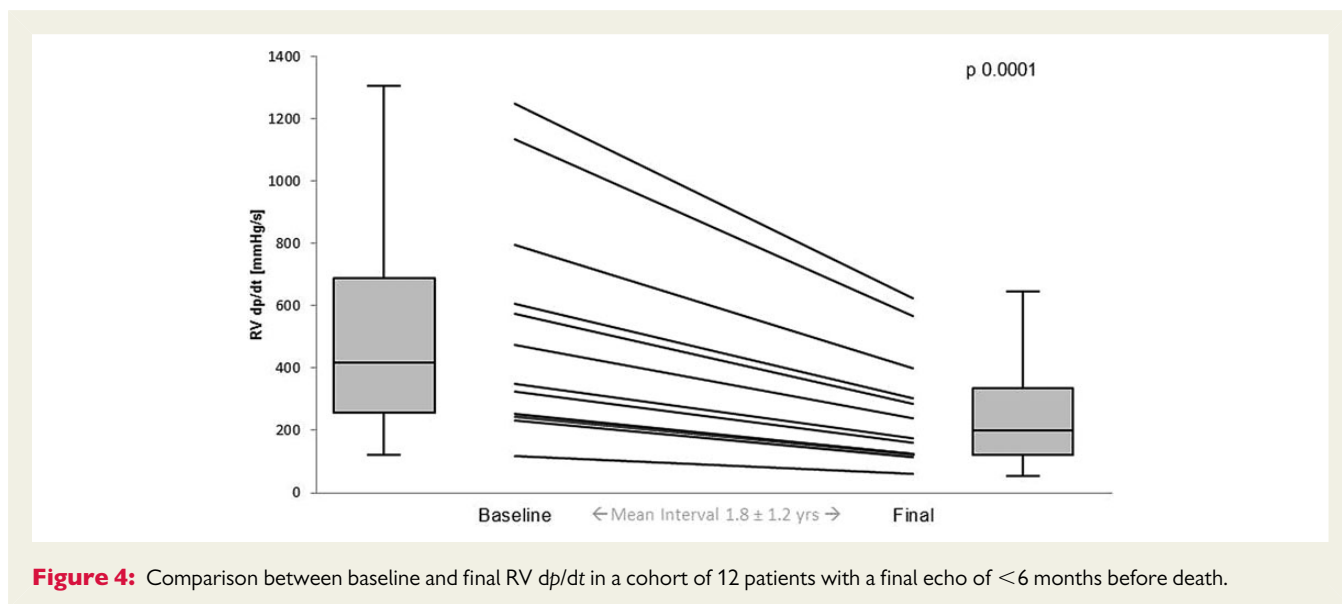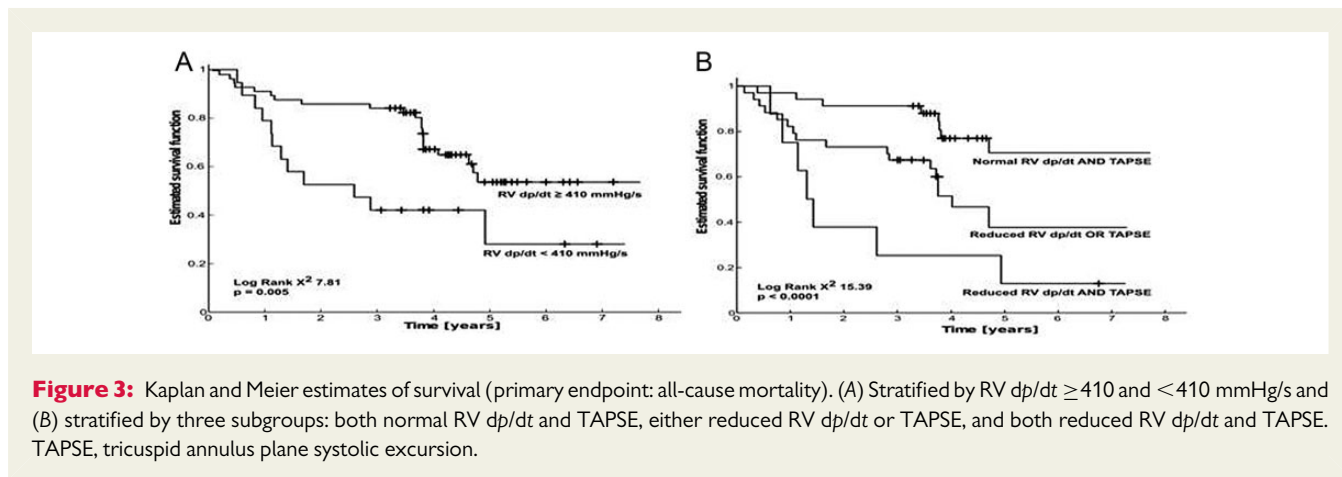
(disease severity, treatment status, and types of PH) and study end-points used.[21] Finally, we did not find major differences with respect to pulmonary pressures or CI when patients were stratified according to normal or reduced RV dp/dt. Indeed, it has been shown previously that invasive haemodynamics correlate with exercise capacity, but are poorly predictive for adverse clinical outcome.[22]

Functional capacity

Our data showed that the proportion of patients with a preserved RV dp/dt was inversely related to NYHA class. Also, RV dp/dt correlated significantly with 6MWD. These results are in line with previous studies showing correlation between RV dp/dt and functional NYHA class in patients with mitral stenosis[23] and also between RV dp/dt/p_{max} and VO$_2$ max in patients with RV failure.[24] It is known that the relationship between RV functional parameters and exercise capacity is not linear in PH due to confounding factors such as impaired pulmonary function, deconditioning, and presence of systemic illness limiting exercise capacity irrespective of RV function. Therefore, previous studies failed to validate a decreased 6MWD as a surrogate for clinical endpoints in patients with PH.[25] Moreover, many RV function parameters including TAPSE have been shown to be loading dependent.[26] However, our attempt to correct for loading by indexation of RV dp/dt to pulmonary pressure or RVEDA did not improve prognostic properties or correlation with functional parameters.

Interobserver variability

We could demonstrate a high level of concordance between observers when RV dp/dt was used as a dichotomous parameter. The percentage interobserver variability was equal to values previously reported for TAPSE.[19] The Bland and Altman plot clearly illustrates that the rather low correlation coefficient was mainly driven by two outliers and by variability in the high normal range of the parameter. This may be because the time measurement in the RV dp/dt denominator becomes less reliable for shorter time intervals, i.e. higher RV dp/dt values. Recalculating Pearson correlation coefficient by excluding two outliers reveals a R-value of 0.81, which is in between values previously reported for TAPSE (R = 0.94) and right ventricular fractional area change (R = 0.64).[4] In summary, discrimination between a preserved and reduced RV dp/dt is easy and reproducible.

due to RV apical rocking, whereas RV dp/dt is not influenced by regional motion.[20]

Our data confirm the validity of NYHA, 6MWD, and RAP as indicators of long-term prognosis in PH.[12] Compared with these predictors, RV dp/dt showed equivalent ROC accuracy and an equally significant hazard ratio (HR). However, our data suggest an added value of RV dp/dt. We therefore propose an echocardiographic model combining TAPSE and RV dp/dt. This model remained an independent predictor of mortality after adjusting for NYHA and 6MWD.

Of note, RAP was associated with a significant HR, but ROC analysis could not demonstrate a significant accuracy to predict 3-year mortality. Indeed, patients with an elevated baseline RAP probably have more profound RV failure and a worse shorter-term prognosis.

Echocardiographic parameters such as Tei index, presence of pericardial effusion, and TR grade were no significant predictors of mortality in our study. Besides that, in previous studies, these parameters did not add prognostic information independent of TAPSE, 6MWD, or NYHA class.[7–11] Conflicting results with previous studies might be explained by marked differences in the study population

Figure 3: Kaplan and Meier estimates of survival (primary endpoint: all-cause mortality). (A) Stratified by RV dp/dt ≥410 and <410 mmHg/s and (B) stratified by three subgroups: both normal RV dp/dt and TAPSE, either reduced RV dp/dt or TAPSE, and both reduced RV dp/dt and TAPSE. TAPSE, tricuspid annulus plane systolic excursion.

Figure 4: Comparison between baseline and final RV dp/dt in a cohort of 12 patients with a final echo of <6 months before death.

Figure 5: Fraction (%) preserved RV dp/dt by NYHA class. NYHA, New York Heart Association.

However, it is difficult to differentiate within the preserved subgroup how good RV contractility actually is. We therefore recommend using RV dp/dt as a dichotomous parameter.

Strengths—limitations—future perspectives

This is, to our knowledge, the largest study in the modern treatment era investigating indicators of prognosis exclusively in newly diagnosed and so far untreated PH patients. The median delay between first diagnosis and baseline ultrasound was only 62 days. This prevented blurring of our results by inclusion of long-term stable patients, which is a major bias of many previous studies in PH. The reliability of the time-to-event analysis was further reinforced by the prolonged minimal follow-up of 3 years with a corresponding mortality rate of 40%. This is in agreement with values previously reported[27] and allowed the use of all-cause mortality as the primary study endpoint. The use of a prospective, high-quality database previously used in several studies offers excellent protection against selection

Figure 6: Interobserver variability. (*A*) Correlation analysis. (*B*) Bland−Altman plot.
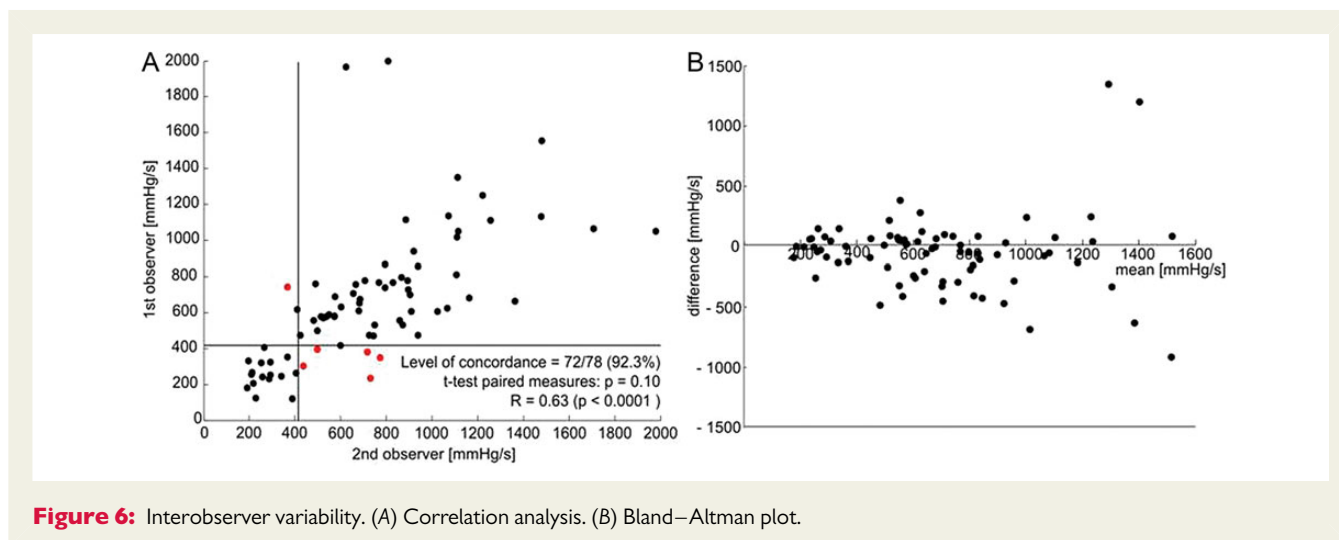
bias due to incompleteness of the database. The retrospective re-analysis of the images excludes the theoretical possibility that knowledge on baseline RV d*p*/d*t* values might have influenced base-line assessment or clinical course of the patients.

A first limitation is that our study population might be enriched by selection bias due to exclusion of eight patients without significant TR. In previous studies, patients with severe TR had a worse prog-nosis. We also excluded operable CTEPH patients since their prognosis is mainly determined by the success of the intervention. Inoperable patients are generally older, have more co-morbidity, and have a worse prognosis.[28] This raises the question whether the prognostic importance of RV d*p*/d*t* would hold among a less ill popu-lation. Secondly, we did not take RAP in to account to determine RV d*p*/d*t*. This is because a previous study found RV d*p*/d*t* to be independent of RAP[13] and because inclusion of RAP would greatly complicate RV d*p*/d*t* assessment and extend the time needed for its calculation. A final remark is that only patients with PAH/CTEPH were included. Future studies are necessary to determine whether our results can be extrapolated to patients with other types of PH- or non-PH-induced RV failure.

Conclusion

RV d*p*/d*t* is easy to obtain and reproducible when used as a dichoto-mous parameter. A reduced baseline RV d*p*/d*t* as a surrogate marker of reduced RV contractility is an independent indicator of poor outcome in patients with PAH/CTEPH. Baseline RV d*p*/d*t* parallels functional capacity as assessed by NYHA and 6MWD. RV d*p*/d*t* can be used with TAPSE, NYHA, and 6MWD for complete non-invasive risk assessment in patients with PH.

Conflict of interest: none declared.

References

1. McLaughlin VV, Presberg KW, Doyle RL, Abman SH, McCrory DC, Fortin T *et al.* Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical prac-tice guidelines. *Chest* 2004;**126**:78S−92S.
2. Bossone E, D'Andrea A, D'Alto M, Citro R, Argiento P, Ferrara F *et al.* Echocardiog-raphy in pulmonary arterial hypertension: from diagnosis to prognosis. *J Am Soc Echo-cardiogr* 2013;**26**:1−14.
3. Haddad F, Hunt SA, Rosenthal DN. Right ventricular function in cardiovascular disease, Part I: anatomy, physiology, aging, and functional assessment of the right ven-tricle. *Circulation* 2008;**117**:1436e48.
4. Forfia PR, Fisher MR, Mathai SC, Housten-Harris T, Hemnes AR, Borlaug BA *et al.* Tricuspid annular displacement predicts survival in pulmonary hypertension. *Am J Respir Crit Care Med* 2006;**174**:1034−41.
5. Van De Bruaene A, De Meester P, Voigt JU, Delcroix M, Pasquet A, De Backer J *et al.* Right ventricular function in patients with Eisenmenger syndrome. *Am J Cardiol* 2012; **109**:1206−11.
6. Ghio S, Recusani F, Klersy C, Sebastiani R, Laudisa ML, Campana C *et al.* Prognostic usefulness of the tricuspid annular plane systolic excursion in patients with congest-ive heart failure secondary to idiopathic or ischemic dilated cardiomyopathy. *Am J Cardiol* 2000;**85**:837−42.
7. Eysmann SB, Palevsky HI, Reichek N, Hackney K, Douglas PS. Two-dimensional and Doppler-echocardiographic and cardiac catheterization correlates of survival in primary pulmonary hypertension. *Circulation* 1989;**80**:353−60.
8. Raymond RJ, Hinderliter AL, Willis PW, Ralph D, Caldwell EJ, Williams W *et al.* Echo-cardiographic predictors of adverse outcomes in primary pulmonary hypertension. *J Am Coll Cardiol* 2002;**39**:1214−9.
9. Tei C, Dujardin KS, Hodge DO, Bailey KR, McGoon MD, Tajik AJ *et al.* Doppler echo-cardiographic index for assessment of global right ventricular function. *J Am Soc Echo-cardiogr* 1996;**9**:838−47.
10. Yeo TC, Dujardin KS, Tei C, Mahoney DW, McGoon MD, Seward JB. Value of a Doppler-derived index combining systolic and diastolic time intervals in pre-dicting outcome in primary pulmonary hypertension. *Am J Cardiol* 1998;**81**: 1157−61.
11. Ghio S, Klersy C, Magrini G, D'Armini AM, Scelsi L, Raineri C *et al.* Prognostic rele-vance of the echocardiographic assessment of right ventricular function in patients with idiopathic pulmonary arterial hypertension. *Int J Cardiol* 2010;**140**: 272−8.
12. Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA *et al.* ESC Committee for Practice Guidelines (CPG). Guidelines for the diagnosis and treat-ment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009;**30**:2493−537.
13. Imanishi T, Nakatani S, Yamada S, Nakanishi N, Beppu S, Nagata S *et al.* Validation of continuous wave Doppler-determined right ventricular peak positive and negative dP/dt: effect of right atrial pressure on measurement. *J Am Coll Cardiol* 1994;**23**: 1638−43.
14. Anconina J, Danchin N, Selton-Suty C, Isaaz K, Juilliere Y, Buffet P *et al.* Noninvasive estimation of right ventricular dP/dt in patients with tricuspid valve regurgitation. *Am J Cardiol* 1993;**71**:1495−7.

15. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2013; **62**(Suppl 25):D34–41.

16. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010; **23**:685–713.

17. Demirkol S, Unlü M, Arslan Z, Baysan O, Balta S, Kurt IH et al. Assessment of right ventricular systolic function with dP/dt in healthy subjects: an observational study. *Anadolu Kardiyol Derg* 2013; **13**:103–7.

18. Rushmer RF, Crystal DK, Wagner C. The functional anatomy of ventricular contraction. *Circ Res* 1953; **1**:162–70.

19. Ernande L, Cottin V, Leroux PY, Girerd N, Huez S, Mulliez A et al. Right isovolumic contraction velocity predicts survival in pulmonary hypertension. *J Am Soc Echocardiogr* 2013; **26**:297–306.

20. Giusca S, Dambrauskaite V, Scheurwegs C, D'hooge J, Claus P, Herbots L et al. Deformation imaging describes right ventricular function better than longitudinal displacement of the tricuspid ring. *Heart* 2010; **96**:281–8.

21. Swiston JR, Johnson SR, Granton JT. Factors that prognosticate mortality in idiopathic pulmonary arterial hypertension: a systematic review of the literature. *Respir Med* 2010; **104**:1588–607.

22. Savarese G, Musella F, D'Amore C, Losco T, Marciano C, Gargiulo P et al. Haemodynamics, exercise capacity and clinical events in pulmonary arterial hypertension. *Eur Respir J* 2013; **42**:414–24.

23. Harati H, Kiavar M, Esmaeizadeh M, Maleki M, Noohi F, Ojaghi Z et al. Correlation of right ventricular dp/dt with functional capacity and RV function in patients with mitral stenosis. *Int Cardiovasc Res J* 2008; **1**:208–15.

24. Kanzaki H, Nakatani S, Kawada T, Yamagishi M, Sunagawa K, Miyatake K. Right ventricular dP/dt/P(max), not dP/dt(max), noninvasively derived from tricuspid regurgitation velocity is a useful index of right ventricular contractility. *J Am Soc Echocardiogr* 2002; **15**:136–42.

25. Gabler NB, French B, Strom BL, Palevsky HI, Taichman DB, Kawut SM et al. Validation of 6-minute walk distance as a surrogate end point in pulmonary arterial hypertension trials. *Circulation* 2012; **126**:349–56.

26. Kass DA, Maughan WL, Guo ZM, Kono A, Sunagawa K, Sagawa K. Comparative influence of load versus inotropic states on indexes of ventricular contractility: experimental and theoretical analysis based on pressure-volume relationships. *Circulation* 1987; **76**:1422–36.

27. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation* 2010; **122**:156–63.

28. Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. *Circulation* 2011; **124**:1973–81.
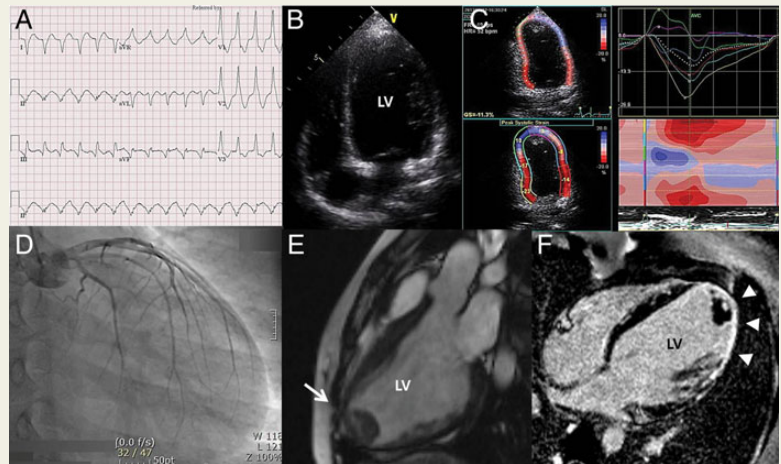
IMAGE FOCUS

An adolescent with laminopathy presenting as ventricular tachycardia and left ventricular apical aneurysm

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A 17-year-old girl was admitted because of recurrent ventricular tachycardia after sudden cardiac arrest (*Panel A*). Two-dimensional and strain echocardiography revealed a dilated left ventricle (LV) with apical aneurysm and dyskinesia (*Panels B* and *C*, and see Supplementary data online, *Video S1*). The normal coronary artery was confirmed under coronary angiography (*Panel D*, and see Supplementary data online, *Videos S2* and *S3*). Cardiac magnetic resonance imaging revealed apical aneurysmal dilatation and wall thinning with thrombus in the LV (*Panel E* and see Supplementary data online, *Video S4*). Subendocardial and transmural late gadolinium enhancement in the LV apical and lateral walls was evident (*Panel F*, arrow heads). An implantable cardioverter-defibrillator was applied in addition to amiodarone, enalapril, carvedilol, and warfarin therapies.

The patient complained of a slowly progressive lower extremity weakness over the past 10 years. She showed a waddling gait, Gower's sign, and Achilles tendon contracture. Under the impression of cardiomyopathy associated with muscular dystrophy, we performed genetic testing, which revealed a mutation (c.1621C>A [p.Arg541Ser]) in the *LMNA* gene.

This is an unusual case of laminopathy presenting as ventricular tachycardia associated with localized myocardial fibrosis and aneurysm.

Supplementary data are available at *European Heart Journal – Cardiovascular Imaging* online.