Relation of Transthoracic Echocardiographic Aortic Regurgitation to Pressure Half-time and All-Cause Mortality

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To evaluate the relation of aortic regurgitation (AR) pressure half-time (PHT) on transthoracic echocardiography (TTE) and all-cause mortality, we screened 118,647 baseline TTE reports from 2000 to 2017, to identify patients with any AR and PHT data. Patients with infective endocarditis or previous aortic valve replacement were excluded. The relation of baseline PHT on time to all-cause mortality was evaluated using Cox regression. A total of 2,653 patients were included (73.1 ± 14.3 years; 53.8% female; PHT, 530 ± 162 ms). Patients with shorter PHTs more frequently had 3-4+ AR (PHT ≤ 200 ms vs > 500 ms, 17.9% vs 0.6%, p < 0.0001). Diastolic parameters (E/e', E/A ratio, mitral valve deceleration time, and pulmonary artery systolic pressure) all significantly correlated with PHT (all p < 0.05). Over a median (IQR) follow-up of 8 (4 to 11 years), there were 799 (30.1%) deaths at a median (IQR) of 1.9 (0.4 to 4.3) years. On a univariate basis, a PHT ≤ 320 ms or > 750 ms was significantly related to increased mortality, even amongst those with nonsevere AR. After multivariable adjustment (in particular for E/e'), PHT was no longer significantly related to death. In conclusion, in this large, single center, retrospective study, AR PHT was not independently related to mortality. While a PHT ≤ 320 ms was associated with increased mortality in patients without severe AR, this relation was no longer significant after adjusting for diastolic functional variables. Thus, a PHT ≤ 320 ms in patients without significant AR may indicate prognostically-relevant diastolic dysfunction. **(Am J Cardiol 2020;135:113−119)**

Since its first use in Doppler ultrasound to quantify the severity of mitral stenosis,[1] the pressure half-time (PHT), the time for the peak pressure difference between 2 cardiac chambers to decay to half of its initial value, has become a fundamental technique in the assessment of valvular disease severity.[2] Based on a close correlation with the degree of invasive angiographic regurgitation, PHT has been used to noninvasively quantify the severity of aortic regurgitation (AR),[3−5] though is influenced by systemic vascular resistance (SVR) and left ventricular (LV) compliance, thus limiting its utility.[6−8] More recently, AR PHT was shown to compare favorably with cardiovascular magnetic resonance (CMR) grading of paravalvular AR in patients with transcatheter aortic valve replacement (TAVR).[9] Despite its frequent use in clinical practice, the relation between PHT and cardiac outcomes, especially mortality, has not been well described with current aortic valve (AV) PHT cut-offs based on historical correlations with AR severity.[3−5] As such, whether existing cut-offs are optimal for identifying patients at high mortality risk remain uncertain. Therefore, we sought to evaluate the relation between PHT and mortality and the determinants of this relation, particularly diastolic function.

Methods

We retrospectively screened 118,647 baseline TTE reports at the Beth Israel Deaconess Medical Center (BIDMC) from January 1, 2000 to December 31, 2017 to identify all reports that included an AR PHT. As part of routine care, TTE data are entered at the time of clinical interpretation into a reporting software and are stored in a large structured electronic database. This database was previously linked to the Social Security Death Master File over the same time period. The database was manually cleaned to remove nonphysiologic measurements with limits decided upon by consensus by 2 National Board of Echocardiography certified physicians prior to the study initiation.

For the current study, only data from an patient's first TTE during the study period was considered. Patients with

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See page 118 for disclosure information.

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missing AR PHT, AV infective endocarditis, no aortic regurgitation, or an aortic valve replacement on baseline TTE were excluded. The study was approved by the BIDMC committee on Clinical Investigation with a waiver of informed consent. The data are available from the corresponding author with a reasonable request.

A list of demographic, physiologic, and echocardiographic variables extracted from baseline TTE reports can be found in **Supplemental eTable 1**. Mitral regurgitation (MR) and AR grades were semiquantitatively graded as 0+ (none), 1+ (mild), 1-2+ (mild to moderate), 2+ (moderate), 3+ (moderate to severe), and 4+ (severe).[2] AR severity grade was determined using an integrative approach as recommended by the American Society of Echocardiography (ASE) guidelines.[2] All measurements were obtained per ASE guidelines.[10–12] Left ventricular ejection fraction (LVEF) was determined using the Simpson's Biplane Method of Discs or 3-dimensional volumetric quantification, when feasible. As AR PHT may be underestimated by nonparallel alignment of the ultrasound beam,[2] it is standard practice at our institution not to record the AR PHT when the peak regurgitant velocity of the continuous-wave Doppler AR envelope is < 4.0 m/s (reflecting a peak diastolic aortic-ventricular pressure gradient < 64 mm Hg). LV diastolic dysfunction grade was not included as it was available in a very small minority (n = 10) and standard grading schema evolved over the course of the study.[13,14] All echocardiographic images were acquired using Vivid 7, Q, 9, I, S70, or e95 echocardiographs and analyzed offline using EchoPAC software (General Electric Healthcare, Waukesha, Wisconsin). The primary outcome was time to all-cause mortality, determined through vital status and date of death information in the linked Social Security Death Master File. Follow-up time was determined as the time from the baseline TTE until the last death date (January 28, 2017) and was complete for all patients.

Detailed statistical methods are provided in **Supplemental eTable 2**. Briefly, to exclude significant selection bias in the inclusion of patients with nonmissing PHT data, baseline characteristics of included patients with available PHT data were compared with characteristics of nonincluded patients with ≥1+ AR and missing PHT data. Baseline characteristics were compared across PHT categories. Pearson correlations were used to evaluate the relation between diastolic parameters and PHT. Kaplan Meier techniques were used to plot time to mortality and a log-rank test used to evaluate for differences across PHT categories. Cox proportional hazards were used to estimate the univariate hazard ratio (HR) for time to mortality, which was modeled against PHT values using restricted cubic splines. As this function was U-shaped with increased mortality risk in the tails of the distribution, we identified the cut-offs of PHT below and above which risk for mortality increased and indicator variables were created for PHT values above and below these cut-offs. Potential confounding variables were sequentially added to nested multivariable Cox proportional hazards models containing these indicator variables to assess the impact of these potential confounders on model results.

Missing observations were categorized in analyses. Analyses were performed with JMP v15.0 and SAS v9.4 (SAS Institute, Cary, North Carolina) using a 2-tailed p-value < 0.05 to declare statistical significance.

To account for the potential influence of the order of variable entry into the model, variables were added 1 at a time to a base model with age, gender, and body surface area (BSA)[15] to assess their impact on the observed results. To additionally parse out the contributions of AR and diastolic function, we evaluated the strength of the observed relations in the subset of patients with < 2+ AR. Third, to verify accuracy of death information, 1 physician (J.B.S.) reviewed the medical charts of a random subset of 20 patients who died to adjudicate death information and ascertain cause of death.

Results

A total of 2,882 baseline TTEs with PHT information were available. Of these, 229 (7.9%) were excluded due to absence of AR or presence of an aortic valve replacement or endocarditis, leaving 2,653 index TTEs on 2,653 patients available for analysis (73.1 ± 14.3 years; 53.8% female; LVEF 55.2% ± 12.3%; PHT 530 ± 162 (range 21to 999 ms). Categorically, a total of 38 patients (1.4%) had a PHT ≤ 200 ms, 1,203 (45.3%) had a PHT 201 to 500 ms, and 1,412 (53.2%) had a PHT > 500 ms. Seventy (2.6%) patients had a bicuspid aortic valve. Included patients with ≥1+ AR and nonmissing PHT data (n = 2,653) were overall similar to nonincluded patients (n = 28,960) with ≥1+ AR and missing PHT data (**Supplemental eTable 3**).

Baseline characteristics by PHT (≤ 200, 201 to 500, and > 500 ms) are summarized in **Table 1**. Compared with those with longer PHTs, those with shorter PHTs were younger (p = 0.004), more frequently male (p < 0.001), inpatient (p < 0.001), had a higher BSA (p < 00001), and a higher heart rate (p < 0.001). Those with shorter PHTs had larger left atrial and LV dimensions, lower LVEF, higher peak AV velocity, greater degrees of pulmonary hypertension (p < 0.05 for all), as well as higher transmitral peak E/A (p = 0.005) and E/e' (p < 0.001) ratios and more frequently had 3-4+ AR (PHT ≤ 200 ms vs > 500 ms, rate of 3% to 4% AR, 17.9% vs 0.6%, p < 0.001).

AR PHT correlated significantly but weakly with diastolic functional variables including E/e' ratio (r = −0.16, 95% CI −0.20 to −0.11, p < 0.001), E/A ratio (r = −0.05, 95% CI −0.09 to −0.02, p = 0.04), transmitral peak E-wave velocity (r = −0.147, 95% CI −0.21 to −0.14, p < 0.001), transmitral E-wave deceleration time (r = 0.09, 95% CI 0.06 to 0.13, p = < 0.001), and peak tricuspid regurgitant gradient (r = −0.20, 95% CI −0.24 to −0.16, p < 0.001).

During a median (interquartile range [IQR]) follow-up of 8[4–11] years, there were 799 (30.1%) deaths, occurring at a median (IQR) of 1.9 (0.4 to 4.3) years after TTE. Of these, 6 (0.8%) occurred in patients with a PHT ≤ 200 ms at a median (IQR) 1.5 (1.3 to 1.7) years, 440 (55.1%) occurred in patients with a PHT 201 to 500 ms at a median (IQR) 1.5 (0.3 to 4.2) years, and 353 (44.2%) occurred in patients with a PHT > 500 ms at a median (IQR) of 1.9 (0.4 to 4.3) years (log rank p = 0.42**).** Using restricted cubic splines, the univariate hazard ratio for increased mortality demonstrated a U-shaped distribution with inflection points for increased mortality (compared with a reference PHT of 500 ms)

Table 1
Baseline characteristics of included patients by Pressure Half-Time (PHT) category

Variable	N obs	Pressure half-time (ms)			
		≤ 200 (n = 39)	201−500 (n = 1,203)	> 500 (n = 1,412)	p-value†
Age (years)*	2,653	69.1 ± 14.8	74.0 ± 14.7	72.4 ± 13.9	0.004
Women	2,652	16 (41.0%)	707 (58.8%)	704 (49.9%)	< 0.001
Inpatient	2,653	22 (57.9%)	650 (54.0%)	612 (43.3%)	< 0.001
Suboptimal Quality	2,653	3 (7.9%)	147 (12.2%)	182 (12.9%)	0.24
Systolic BP (mm Hg)	2,610	126.7 ± 20.8	131.8 ± 22.2	132.7 ± 21.1	0.17
Diastolic BP (mm Hg)	2,606	70.3 ± 12.1	68.5 ± 14.0	72.4 ± 12.7	< 0.001
Heart rate (bpm)	2,372	73.1 ± 16.6	74.7 ± 13.8	67.1 ± 13.1	< 0.001
Height (cm)	2,556	169.6 ± 7.4	164.9 ± 11.1	166.4 ± 11.4	< 0.001
Weight (kg)	2,611	76.7 ± 14.3	71.0 ± 18.1	74.0 ± 17.2	< 0.001
Body surface area (m^2)	2,547	1.91 ± 0.18	1.79 ± 0.26	1.84 ± 0.26	< 0.001
Body mass index (kg/m^2)	2,547	27.1 ± 5.1	26.0 ± 5.7	26.7 ± 5.3	0.01
Left atrial dimension (cm)					
Anteroposterior	2,579	4.3 ± 0.7	4.1 ± 0.8	4.0 ± 0.8	0.004
	2,608	5.6 ± 0.8	5.4 ± 0.9	5.3 ± 0.9	0.09
Superoinferior					
Right atrial superoinferior dimension (cm)	2,743	5.3 ± 0.7	5.1 ± 0.9	5.1 ± 0.8	0.19
Left ventricular dimension (cm)					
End-diastolic	2,585	4.9 ± 1.0	4.7 ± 0.8	4.5 ± 0.7	< 0.001
End-systolic	1,872	3.3 ± 1.2	2.9 ± 0.9	2.9 ± 0.7	0.003
Left ventricular wall thickness (cm)					
Septal	2,589	1.2 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	0.47
Inferolateral	2,584	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	0.36
Left ventricular ejection fraction (%)	2,647	49.4 ± 16.5	54.3 ± 13.3	56.2 ± 11.1	< 0.001
Aortic valve peak velocity (m/s)	2,532	2.2 ± 1.2	2.2 ± 1.1	1.9 ± 0.9	< 0.001
Aortic valve mean gradient (mm Hg)	765	29.9 ± 20.4	28.9 ± 19.4	24.4 ± 18.3	0.004
Aortic valve area (cm^2)	593	1.4 ± 0.8	1.1 ± 0.4	1.2 ± 0.6	< 0.001
Bicuspid aortic valve	2,653	2 (5.3%)	28 (2.3%)	40 (2.8%)	0.43
Aortic valve pressure half time (ms)	2,653	131 ± 59	402 ± 70	650 ± 114	< 0.001
Aortic regurgitation grade	2,653				< 0.001
1+		27 (71.1%)	685 (56.9%)	1,134 (80.3%)	
1-2+		1 (2.6%)	290 (24.1%)	210 (14.9%)	
2+		3 (7.9%)	179 (14.9%)	60 (4.3%)	
3+		3 (7.9%)4	34 (2.8%)	5 (0.4%)	
4+		(10.5%)	15 (1.3%)	3 (0.2%)	
Peak transmitral E-wave velocity (m/s)	2,546	1.0 ± 0.4	1.0 ± 0.3	0.8 ± 0.3	< 0.001
Peak transmitral A-wave velocity (m/s)	2,283	0.8 ± 0.4	0.9 ± 0.3	0.8 ± 0.3	< 0.001
Mitral E-wave deceleration time (ms)	2,401	198 ± 90	218 ± 73	235 ± 72	< 0.001
Mitral peak E/A ratio	2,282	1.3 ± 0.7	1.2 ± 0.7	1.1 ± 0.6	0.004
Average E/e'	1,683	14 ± 10	13 ± 6	11 ± 5	< 0.001
Tissue Doppler mitral annulus (cm/s)					
Lateral	1,728	9.4 ± 5.6	8.7 ± 3.1	9.8 ± 7.8	0.52
Septal	1,726	8.1 ± 3.6	6.9 ± 2.6	6.9 ± 2.4	0.07
Mitral regurgitation grade	2,369				< 0.001
0+		0%	22 (1.8%)	32 (2.3%)	
1+		26 (66.7%)	701 (58.3%)	1104 (78.2%)	
1-2+		4 (10.3%)	152 (12.6%)	130 (9.2%)	
2+		6 (15.4%)	118 (9.8%)	76 (5.4%)	
3+		0%	48 (4.0%)	26 (1.8%)	
4+		0%	15 (1.2%)	9 (0.6%)	
Peak tricuspid regurgitant gradient (mm Hg)	2,194	34 ± 13	33 ± 12	29 ± 10	< 0.001

BP = blood pressure; obs = observations; PHT = aortic valve pressure half-time; SD = standard deviation.

* Values represents means ± standard deviations unless otherwise stated.

† Represents the p-value for the comparison across PHT categories using ANOVA for continuous variables and the Chi Squared test for categorical variables.

below 320 ms and above 750 ms (**Figure 1**). The lowest mortality risk was observed at a PHT of 620 ms. Specifically, compared with a PHT of 321 to 750 ms a PHT of ≤ 320 ms was associated with a 54% increased risk of mortality (HR 1.54, 95% CI 1.22 to 1.94, p < 0.001) and a PHT > 750 ms was associated with a 58% increased risk of mortality (HR 1.58, 95% CI 1.17 to 2.14, p = 0.003). Thus, PHT appeared to have a U-shaped relation with death occurring in 80 (36.9%) patients with a PHT ≤ 320 ms at a median (IQR) of 1.0 (0.2 to 2.3) years, 674 (30.9%) patients

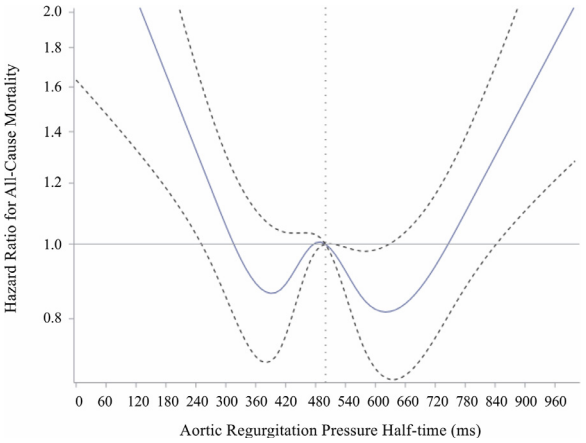

Figure 1. Proportional hazards regression using restricted cubic splines to model the relationship of hazard ratio of all-cause mortality and aortic regurgitation pressure half-time. Relation of the hazard ratio for all-cause mortality (y-axis) and baseline aortic regurgitation pressure half-time (x-axis) in milliseconds. The horizontal gray line indicates the null value (a hazard ratio of 1.0). The vertical dashed line indicates the reference PHT value of 500 ms. The blue solid line indicates the point estimate for hazard ratio at each PHT value and the dashed gray lines indicate the 95% confidence interval for the hazard ratio estimates.

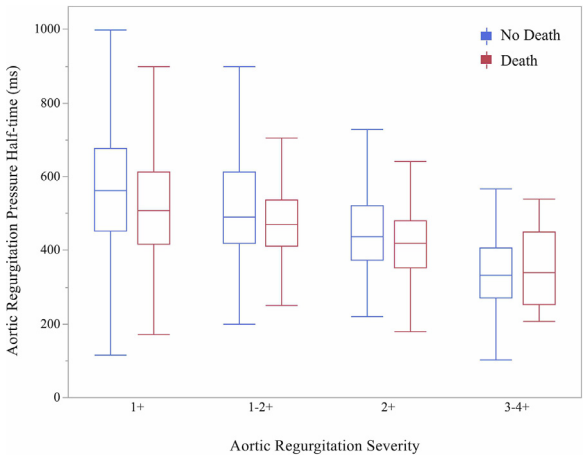

Figure 3. Boxplots displaying pressure half-time distributions by AR severity and mortality

Displayed is the AR PHT (Y-axis) according to AR severity (X-axis) and mortality. Box-plots indicated in red show the distribution of AR PHT amongst patients who died and box-plots in blue show the distribution of AR PHT amongst survivors. Boxes represent the interquartile range and whiskers represent the range of values for AR PHT. PHT values were lower amongst patients who died for all grades of AR ($p < 0.05$ for all) except 3-4+ AR ($p = 0.97$).

with a PHT 321 to 740 ms at a median (IQR) of 2.2 (0.5 to 4.8) years, and 45 (17.7%) patients with a PHT > 750 ms at a median (IQR) of 0.8 (0.3 to 3.0) years (**Figure 2**; log rank $p < 0.001$). Within each grade of AR severity, except for 3-4+ AR ($p = 0.97$), the AR PHT was lower in patients who died ($p < 0.05$ for all; **Figure 3**).

Multivariable adjusted results evaluating the relation of PHT ≤ 320 ms and > 750 ms on time to mortality are provided in **Tables 2-3** respectively. The adjusted relation of PHT ≤ 320 ms and time to mortality persisted despite adjustment for age, gender, BSA, AR severity, systolic and diastolic BP, LVEF, heart rate, inpatient status, image quality, AV peak velocity, LV diastolic dimension, and peak TR gradient (adjusted HR 1.40, 95% CI 1.04 to 1.89, $p = 0.03$). However, the relation became nonsignificant after adjustment for E/e'. The adjusted relation of PHT > 750 ms and time to mortality persisted despite adjustment for age, gender, BSA, AR severity, systolic and diastolic BP, and LVEF (adjusted HR 1.58, 95% CI 1.14 to 2.19, $p = 0.006$) but became nonsignificant with the addition of heart rate ($p = 0.053$) and subsequent

In sensitivity analysis, the adjusted relation of PHT ≤ 320 ms on mortality was robust to all variables except LV end-diastolic diameter for E/e' (**Supplemental eTable 4**). In contrast, the adjusted relation of PHT > 750 ms with mortality became nonsignificant with the addition of variables related to patient acuity (i.e., heart rate, inpatient

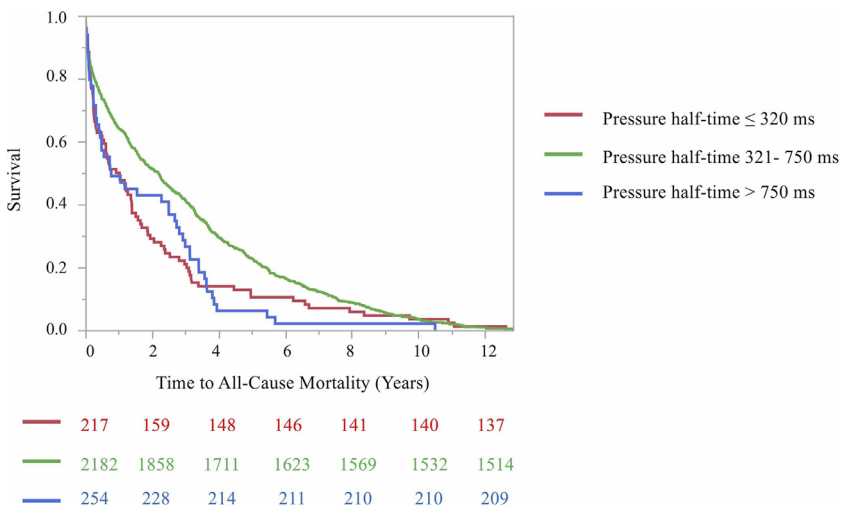

Figure 2. Kaplan Meier curves demonstrating survival by AR pressure half-time category. Kaplan-Meier plot of time to all-cause mortality in years according to baseline pressure half-time category. Numbers below the graph indicate the number in the risk set at each 2-year interval. Estimates are truncated at 12 years. The median (interquartile range) of time to mortality was 0.8 (0.3 to 3.0) years in patients with a PHT > 750 ms (blue line), 2.2 (0.5 to 4.8) years in patients with a PHT 321 to 750 ms, and 1.0 (0.2 to 2.3) years in patients with a PHT ≤ 320 ms (log rank p-value < 0.001)

Table 2
Results of nested multivariable models evaluating impact of a PHT ≤ 320 ms on time to all-cause mortality

Model	Description	Hazard ratio	95% CI	p-value
1	Unadjusted	1.54	1.22−1.94	0.0003
2	Model 1 + age, sex, BSA	1.75	1.37−2.23	< 0.001
3	Model 2 + AR severity	1.76	1.38−2.25	< 0.001
4	Model 3 + systolic and diastolic BP	1.69	1.32−2.17	< 0.001
5	Model 4 + LVEF	1.70	1.33−2.19	< 0.001
6	Model 5 + heart rate	1.39	1.07−1.81	0.01
7	Model 6 + inpatient status	1.36	1.04−1.89	0.02
8	Model 7 + image quality	1.39	1.07−1.82	0.02
9	Model 8 + AV peak velocity	1.39	1.06−1.83	0.02
10	Model 9 + LV end-diastolic diameter	1.37	1.04−1.80	0.02
11	Model 10 + TR gradient	1.40	1.04−1.89	0.03
12	Model 11 + E/e'	0.96	0.62−1.49	0.74
13	Model 12 + MR severity	0.79	0.49−1.28	0.35

AR = aortic regurgitation; AV = aortic valve; BP = blood pressure; BSA = body surface area; CI = confidence interval; LVEF = left ventricular ejection fraction; LV = left ventricular; MR = mitral regurgitation; TR = tricuspid regurgitant.

Effect of the addition of sets of variables to the unadjusted proportional hazards model evaluating a pressure half-time ≤ 320 ms compared with a PHT 321-750 ms and time to mortality.

status) (**Supplemental eTable 5**). In those with an AR grade < 2+ (n = 2347), PHT ≤ 320 ms was associated with a 72% increased risk of mortality (HR 1.72, 95% CI 1.30 to2.27, p < 0.001) and PHT > 750 ms was associated with a 51% increased risk of mortality (HR 1.51, 95% CI 1.09 to 2.09 = 0.01) after adjusting for age, gender, and BSA (PHT 321 to 750 as reference).

Review of the medical charts of a subset of 20 patients to adjudicate death information and ascertain cause of death demonstrated death information was available in 19/20 (95%) and date of death was accurate in all cases. Causes of death by PHT category are listed in **Supplemental eTable 6**

Table 3
Results of nested multivariable models evaluating impact PHT > 750 ms on time to all-cause mortality

Model	Description	Hazard ratio	95% CI	p-value
1	Unadjusted	1.58	1.17−2.14	0.003
2	Model 1 + age, sex, BSA	1.52	1.10−2.09	0.01
3	Model 2 + AR severity	1.52	1.10−2.10	0.01
4	Model 3 + systolic and diastolic BP	1.55	1.12−2.15	0.008
5	Model 4 + LVEF	1.58	1.14−2.19	0.006
6	Model 5 + heart rate	1.39	1.00−1.94	0.053
7	Model 6 + inpatient status	1.33	0.95−1.85	0.10
8	Model 7 + image quality	1.30	0.93−1.82	0.12
9	Model 8 + AV peak velocity	1.26	0.90−1.77	0.18
10	Model 9 + LV end-diastolic diameter	1.25	0.88−1.78	0.20
11	Model 10 + TR gradient	1.16	0.79−1.71	0.45
12	Model 11 + E/e'	1.07	0.66−1.73	0.78
13	Model 12 + MR severity	1.56	0.89−2.73	0.12

AR = aortic regurgitation; AV = aortic valve; BP = blood pressure; BSA = body surface area; CI = confidence interval; LVEF = left ventricular ejection fraction; LV = left ventricular; MR = mitral regurgitation; TR = tricuspid regurgitant.

Effect of the addition of sets of variables to the unadjusted proportional hazards model evaluating a pressure half-time > 750 ms compared with a PHT 321-750 ms and time to mortality.

Discussion

In this large single-center, retrospective, multidecade echocardiographic study, AR PHT was not related with mortality after multivariable adjustment. While a PHT ≤ 320 ms was associated with an increased risk of mortality even amongst those with nonsevere AR, this relation was no longer significant after adjusting for diastolic functional variables. Taken together, these data suggest that a PHT ≤ 320 ms in those without significant AR may indicate prognostically-relevant diastolic dysfunction but should be confirmed in independent study.

Starting with catheterization experiments in the 1970s, the rate of the pressure decline between the aorta and LV has been a reliable and specific metric for chronic AR, varying inversely with angiographic AR grade.[16,17] With the development and use of Doppler ultrasound for valvular assessment,[3,18] it was noted that angiographic and Doppler PHT values were closely correlated (r = 0.91), prompting enthusiasm for use in grading AR.[4,5,19,20] However, the dependence of this relation on aortic and LV compliance and systemic vascular resistance has limited use of PHT as the primary method for AR quantification in practice.[6−8,21,22] Specifically, PHT has been noted to vary inversely with AR severity and directly with systemic vascular resistance, aortic, and LV compliance.[7,8] Exploiting this relation, Yamamoto et al.[23] found that AR PHT estimation of LV relaxation (using -dP/dt) in dogs with acute ischemia correlated better with catheter-derived measures of tau, the time constant for LV relaxation, than did similar measures using MR. Additional limitations of the PHT method include the need for parallel insonation with the AR jet to avoid miscalibration of AR severity.[6] Owing to the introduction of other techniques and imaging types for assessing AR severity, PHT remains only a piece of the armentarium, for global assessment of AR severity.[2]

Despite widespread reporting of AR PHT, to our knowledge, our study is the first to report a relation between PHT and all-cause mortality. Overall, after multivariable adjustment, PHT was not related to mortality. The univariate relation between PHT and mortality was U-shaped with those having a PHT ≤ 320 ms or PHT > 750 ms having an elevated risk for mortality compared with those with an AR PHT 321-750 ms, even in those with nonsignificant AR. However, the relation of PHT > 750 ms and mortality became no significant after adjustment for inpatient status, heart rate, and E/e', suggesting confounding by patient acuity. In contrast, the relation of PHT ≤ 320 ms and mortality persisted despite adjustment for inpatient status, AR grade, BP (a surrogate for systemic vascular resistance), and image quality, but became nonsignificant with inclusion of E/e', suggesting that the relation of a low PHT and mortality (particularly in the absence of significant AR) may be mediated by diastolic dysfunction. Supportive of this hypothesis is the significant but weak negative correlation between AR PHT and E/e' ratio, transmitral E/A ratio, peak transmitral

E-wave velocity, and peak tricuspid regurgitant gradient, and positive correlation with mitral valve E-wave deceleration time, suggesting a relation between shorter PHTs and worsened diastolic function. As diastolic grade was available only in a small subset (and the grading scheme varied over the course of the study), it is not possible to directly correlate diastolic grade and PHT in the current study. Although further research is needed to confirm this relation, these findings support the possibility of a PHT ≤ 320 as a potential marker of prognostically significant diastolic dysfunction.

While the rate of 3-4+ AR was indeed higher in those with a PHT ≤ 200 ms compared with > 500 ms (17.9% vs 0.6%), upwards of 82% of those with a PHT ≤ 200 ms had nonsevere (i.e., < 3-4+) AR, thus challenging the specificity of a low PHT for severe AR. Rather, these findings suggest that the AR PHT needs to be considered within the context of the rest of the available data on AR severity, LV compliance, and BP. Indeed, other studies have also indicated the low predictive value of PHT for severe AR in the setting of abnormal LV relaxation.[24,25]

Our findings have a number of implications for the use and interpretation of PHT in practice. First, they suggest that a low PHT (particularly ≤ 320 ms) may indicate adverse risk independent of AR severity, possibly mediated by diastolic dysfunction. Second, they suggest a role for routine reporting of PHT in clinical practice whenever feasible. Third, they extend observations on the lack of reliability of PHT for AR grading and suggest that even low values of PHT may not be specific for severe AR.

There are some limitations to the study. First, as a retrospective study, causality cannot be inferred with the current techniques. Second, findings should be confirmed by independent study. Third, detailed quantitative information (e.g., vena contracta and effective regurgitant orifice area) were not available and could influence the relation of AR and PHT.[2] Fourth, it is possible that the observed effect is mediated by unmeasured clinical variables. Nevertheless, the AR PHT may still have value as a risk marker. Finally, information on aortic compliance was not available, though adjustment for BP, as a surrogate for SVR and aortic compliance, did not impact results.

In conclusion, in this large multidecade retrospective single center study, AR PHT was not related to mortality on multivariable analysis. While a PHT ≤ 320 ms was associated with adverse mortality risk, even amongst patients with nonsevere AR, this relation was no longer significant after adjustment for the diastolic functional variables. Thus, a PHT ≤ 320 ms in patients without significant AR may indicate prognostically-relevant diastolic dysfunction, though should be confirmed in independent study.

Authors contribution

Jordan B. Strom: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Visualization, Writing - original draft. Writing - review & editing; **Eli V. Gelfand**: Investigation, Methodology, Writing - review & editing; **Lawrence J. Markson**: Data curation, Project administration, Resources, Software, Writing - review & editing; **Connie A. Tsao:** Formal analysis, Investigation, Methodology, Visualization, Writing - review & editing; **Warren J. Manning:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Writing - review & editing.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

Disclosures

All other authors report no disclosures.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.08.043.

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