

Original Article

Echocardiographic transmitral inflow ascending arm shows two slopes in health and heart failure: a novel phenomenon

Muhammad A Egbaria¹, Shemy Carasso^{3,4}, Muhamed Jabaren², Guy Dori^{1,5}

Departments of ¹Internal Medicine E, ²Cardiology, Emek Medical Center, Afula 18101, Israel; ³Department of Cardiology, The Baruch Padeh Medical Center, Poriya, Israel; ⁴Faculty of Medicine, Bar-Ilan University, Zefat Campus, Zefat, Israel; ⁵Faculty of Medicine, Technion- Israel Institute of Technology, Haifa, Israel

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Abstract: Few studies have focused on the ascending arm of the transmitral valve inflow Doppler E wave signal (EWAA), measured in standard echocardiographic examinations. After measuring the slopes, frequencies of 1- and 2-slope EWAA were calculated for 3 study groups, including the healthy controls (HC), subjects with risk factors for heart failure with preserved ejection fraction (HFPEF-RF), and patients with HFPEF. Investigators were blinded to the association between the study group and echocardiographic examinations. The study groups, HC, HFPEF-RF, and HFPEF, included 57, 60, and 66 subjects, respectively. There were 166, 161, and 199 E waves available for analysis in HC, HFPEF-RF, and HFPEF groups, respectively. Prevalence levels of the 2-slope EWAA in HC, HFPEF-RF, and HFPEF groups were 38%, 39%, and 46%, respectively ($P < 0.22$). When 2-slope EWAA was detected, the value of the early slope was 34-50% greater than that measured when a single slope was detected ($P < 0.001$). Results suggest that the 2-slope EWAA phenomenon is common and may be related to forces driving blood from the left atrium to left ventricle. Mechanisms underlying the 2-slope EWAA phenomenon, however, have yet to be revealed.

Keywords: Heart failure with preserved ejection fraction, diastolic heart failure, transmitral inflow, E wave

Introduction

E wave, the first trans-mitral flow velocity signal, reflects early left ventricle (LV) filling. It was recently determined as one of four measured variables necessary for evaluation of diastolic function in patients with normal LV ejection fraction [1]. The E wave is a triangular signal with an ascending arm (E wave ascending arm, EWAA), culminating at the peak velocity of blood flow, and a descending arm, demonstrating how mitral inflow decelerates.

Each point on the EWAA signal (measured with Doppler) is the instantaneous velocity of a blood sample crossing the mitral valve orifice in units of cm/sec. The slope of the EWAA (s-EWAA) reflects blood acceleration in units of cm/sec². If the EWAA is observed as a straight line, starting at zero velocity and culminating at peak E wave, blood acceleration is constant. If blood acceleration is constant, according to

Newton's second law of motion, $\Sigma F_i = M \cdot a$, where ΣF_i is the sum of all forces acting on blood mass M and a is the acceleration of M , then ΣF_i must be constant as well. A force acting on a surface equals pressure. Thus, ΣF_i can be replaced with $\Sigma P_i(t) \cdot MVA(t)$, where $P_i(t)$ is the i -th pressure contribution affecting blood mass M . $MVA(t)$ is the mitral valve area or cross-section, both depending on t , the time duration interval of EWAA. $\Sigma P_i(t)$ is the instantaneous pressure gradient between the left atrium (LA) and the LV, (LA-LV) PG, during EWAA. Previous studies have provided knowledge regarding blood propelling forces [2, 3], along with the effective MVA during early diastole [4]. The physiology underlying a 1-slope EWAA (constant acceleration) necessitates a constant product $\Sigma P_i(t) \cdot MVA(t)$ during EWAA. For example, when (LA-LV) PG causes the mitral valve to open, MVA increases abruptly. To maintain a constant product, the (LA-LV) PG must decrease proportionately to the rapid increase of MVA. (LA-LV) PG rapidly decreases

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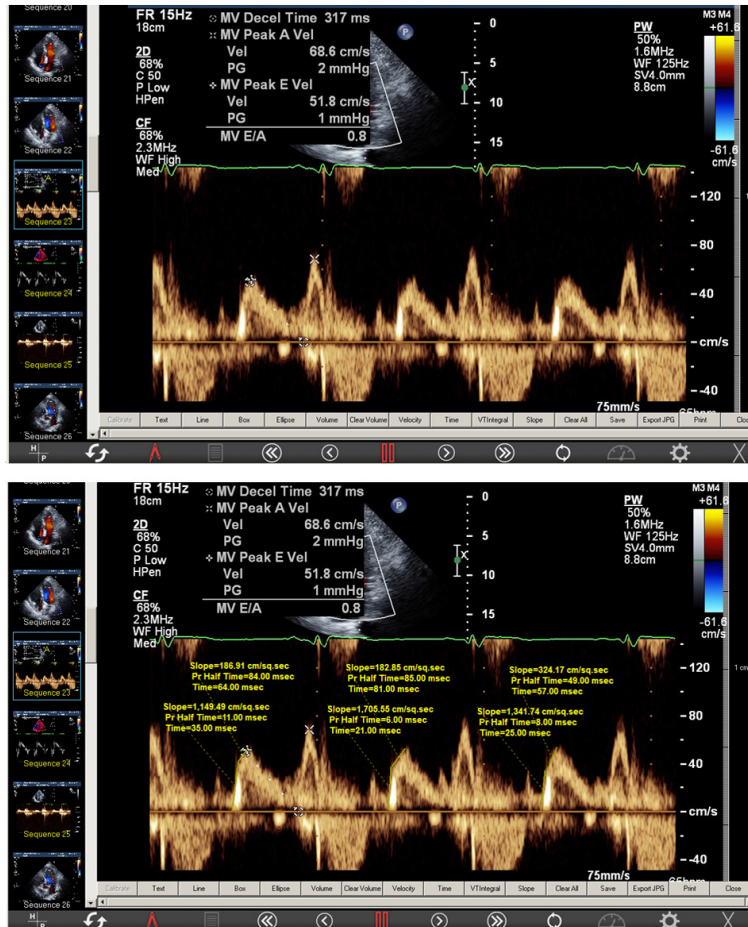


Figure 1. Trans-mitral flow velocity signals. Upper panel displays original recordings. Lower panel displays the superimposed measurements of slopes of EWAA. All 3 E waves display an ascending arm with 2 slopes.

due to the transfer of blood volume from the LA to the LV, resulting in a decrease in LA pressure and an increase in LV pressure. Alternatively, when a blood driving force decreases during the EWAA (e.g., a decay of the elastic restoring force) while MVA is constant or decreasing, acceleration must decrease, respectively. This scenario imposes a change on s-EWAA. There are few studies considering EWAA [5, 6]. To the best of our knowledge, the phenomenon of an EWAA with two slopes has not been previously described, despite the fact that it is not difficult to detect by eye-ball examination two slopes in E wave signals. For example: Ref. 1, Figure 7, middle panel, second E wave from left; Figure 23, top right, first E wave from left On website: <http://www.criticalecho.com/see> tutorial number 8: Assessment of LV diastolic function and filling pressures. Go to Figure 2 first E wave from left.

The present study focused on s-EWAA, assuming that it may not be constant. Two slopes on the EWAA may be visually observed. In a blinded fashion, slopes of EWAA were retrospectively analyzed for three subject groups, including healthy controls (HC), healthy individuals with risk factors for heart failure with preserved ejection fraction (HFPEF-RF), and HFPEF patients. For every EWAA examined, investigators determined whether 1 or 2 slopes were present and slope values were measured. It was hypothesized that, in HFPEF patients, a 2-slope EWAA would be more prevalent than in HFPEF-RF or the HC groups. This hypothesis was based on a previous hypothesis suggesting a benefit for recruiting elastic recoil to augment early diastolic filling, compensating for decreased late LV filling due to LV stiffness in HFPEF [6]. Moreover, Bell et al. showed that most of the elastic recoil terminates before mitral valve opening [7]. It was, therefore, hypothesized that termination of elastic recoil during the EWAA

may explain an observed change in blood acceleration, creating a 2-slope EWAA. However, it must be emphasized from the onset that this preliminary descriptive study aimed to suggest the presence of a phenomenon, namely that EWAA may attain 2 slopes. The present study was not designed, however, to investigate the underlying mechanisms.

Materials and methods

Subjects

The present study was approved by the Institutional Review Board of Emek Medical Center, as a retrospective study.

HFPEF patients and subjects with HFPEF-RF were included based on clinical criteria. HFPEF inclusion criteria: A) Patients were hospitalized due to heart failure, according to a list of diag-

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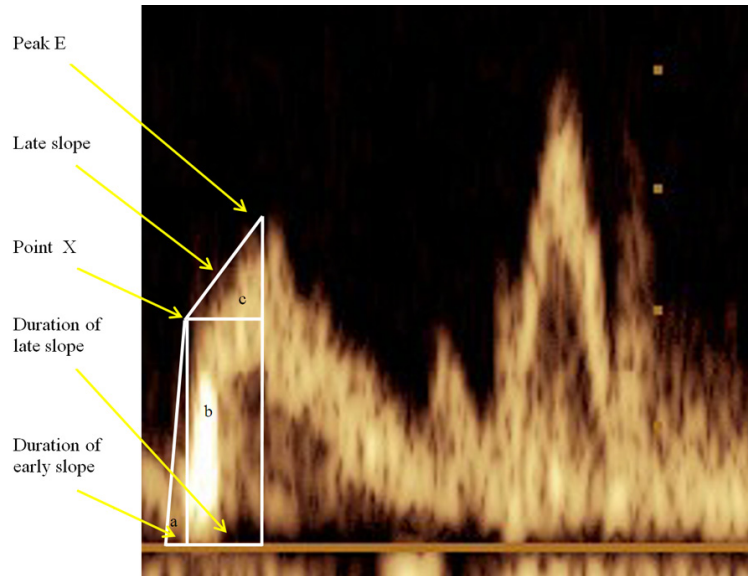


Figure 2. Area bounded between a 2-slope EWAA and the zero velocity line. Areas of triangles a and c are calculated from the height of the triangle multiplied by the base of the triangle divided by 2. Area of triangle a equals the product of the duration of the early slope in msec/1000 (base of triangle a) by the height of triangle a given by the product of the early slope in cm/sec² and the duration of the early slope (point X in **Figure 2**), divided by 2. Area of rectangle b equals the product of the duration of the late slope by X. Area of triangle c equals product of the duration of the late slope in msec/1000 (base of triangle c) by the height of triangle c, given by the product of the late slope in cm/sec² multiplied by the duration of the late slope, divided by 2. In these calculations the unit of all areas was cm, because all values of height were measured in cm/sec and all bases were measured in sec.

1- and 2-slope EWAA (per wave analysis)

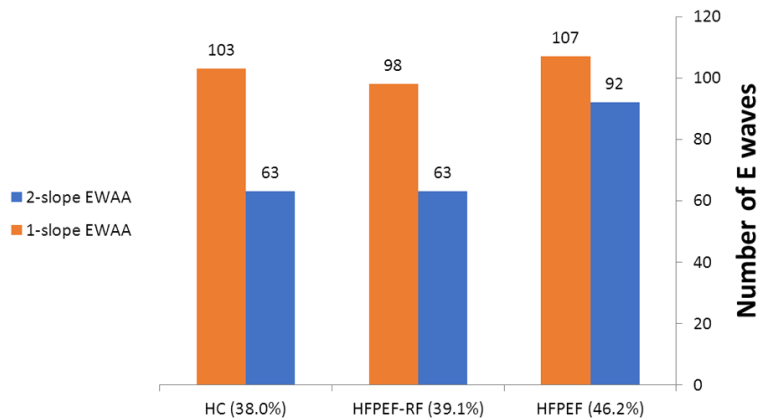


Figure 3. Number of 1- and 2-slope EWAA in each of the study groups (per wave analysis). Below the abscissa, the percent value indicates the percent of EWAA having 2-slopes.

noses on electronic medical records; and B) Patients had a trans-thoracic echocardiographic examination demonstrating ejection fraction $\geq 50\%$, within a period of 30 days between hos-

pitalization and the echocardiographic study. HFPEF-RF inclusion criteria: A) Patients were never hospitalized for heart failure (according to electronic medical records); B) Patients had an ambulatory trans-thoracic echocardiographic examination, concluded as normal, demonstrating ejection fraction $\geq 50\%$; and C) Patients had at least one of the following diagnoses, including hypertension, diabetes mellitus, or ischemic heart disease, or any two or more of the following diagnoses, including hyperlipidemia, cigarette smoking, chronic obstructive pulmonary disease, and obesity.

Healthy control (HC) group inclusion criteria: A) Patients had an ambulatory trans-thoracic echocardiographic examination, concluded as normal, demonstrating ejection fraction $\geq 50\%$; and B) Patients had only one of the following risk factors, including hyperlipidemia, obesity, smoking, or chronic obstructive pulmonary disease.

Exclusion criteria: A) Patients were excluded if valvular pathologies were greater than mild; B) Structural cardiac abnormalities, arrhythmias, or cardiac operations were noted on their list of diagnoses or echocardiographic examination reports; and C) Lack of P waves existing on the ECG recorded during echocardiographic examinations.

The Data Mining and Information Unit provided investigators with a single shuffled list of identity numbers of subjects from all study groups. During analyses of subject s-EWAA results, investigators were blinded to the electronic medical records and clinical groups.

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Table 1. Demographic, clinical, and basic echocardiographic characteristics of study groups

	HC (n=57)	HFPEF-RF (n=60)	HFPEF (n=66)	P
Age (years)	59.9±15.3	68.0±10.2	65.8±13.1	0.0028
Female-gender (%)	20 (35.1%)	26 (43.3%)	28 (42.4%)	0.6082
Hypertension (%)	0 (0%)	49 (81.67%)	55 (83.3%)	<.0001
Diabetes Mellitus (%)	0 (0%)	14 (23.3%)	35 (53.0%)	<.0001
Ischemic heart disease (%)	0 (0%)	8 (13.3%)	9 (13.6%)	0.0144
Hyperlipidemia (%)	12 (21%)	36 (60.0%)	39 (59.1%)	<.0001
Obesity (%)	6 (10.5%)	12 (20.0%)	20 (30.3%)	0.0260
Cigarette smoking (%)	0 (0%)	3 (5.0%)	10 (15.2%)	0.0023
COPD (%)	0 (0%)	2 (3.3%)	9 (13.6%)	0.0028
E wave (cm)	66.3±20.6	58.6±26.7	77.6±24.8	0.002
A wave (cm)	70.9±24.9	78.2±34.3	87.2±26.5	0.001
E/A	0.97±0.2	0.79±0.2	0.89±0.3	<0.001
EF (%)	63.4±4.1	63.0±4.6	62.3±5.4	0.32
IVS (cm)	9.9±1.2	10.6±1.4	11.9±1.6	<0.001
PW (cm)	9.8±1.0	10.3±1.4	11.4±1.5	<0.001

Cm, centimeters; COPD, chronic obstructive pulmonary disease; IVS, interventricular septum; PW, posterior wall; other abbreviations as in text. Pairwise comparisons (Bonferroni's correction) revealed no significant differences between HFPEF-RF and HFPEF (except for diabetes mellitus, $P=0.0006$). Between HFPEF-RF and HC, significant differences were found for age ($P=0.0011$), ischemic heart disease ($P=0.0062$), diabetes mellitus ($P=0.0001$), Hyperlipidemia ($P<.0001$), and Hypertension ($P<.0001$). Between HFPEF and HC, significant differences were found for all factors ($P<0.02$). Echocardiographic characteristics were tested using Kruskal-Wallis, as distribution of variables differed from the normal distribution.

Study protocol

Two investigators (M.A.E., G.D.) received the shuffled list of identity numbers of included subjects. For each echocardiographic study, images displaying the trans-mitral flow velocity were sought and EWAAAs were analyzed, as described below. All analyzed data were agreed upon before disclosing the association between subject's echocardiographic study and clinical group. Demographic and clinical data were retrieved from electronic medical records. Final association and statistical analysis was then performed.

Echocardiography

Standard echocardiographic analysis of diastolic measures was performed by an echocardiography specialist (M.J.), blinded to the rest of the analyses. Measures are reported in **Table 1**.

1) Measurements of slope and slope duration: For each echocardiographic study, the EWAAAs (**Figure 1**) were analyzed. The ascending arms

of the E waves were measured by two independent observers (M.A.E., G.D.). These investigators were blinded to the other's measurements. The number of available E waves per patient was documented, as well as the sequence of the waves in the image. Using this documentation, the "second" investigator could relate to the same EWAA evaluated by the "first", however, remaining completely blinded to the measurements of the first. Slopes of EWAA were measured using the "slope" function of the archiving software (PICOM PowerConsole version 5.24.0.38, ScImage Inc., Los Altos, California). When 1-slope EWAA was detected, the slope was measured from the peak of the E wave to the zero velocity line (in cm/sec^2). Attention was paid to align the measuring line with the

contour of the EWAA. When 2 slopes were detected, the first slope was measured from the peak of the E wave to the point where slope deflection was observed. This slope was termed late s-EWAA. From the latter point, the second slope, termed early s-EWAA, was measured to the zero velocity line. **Figure 1** (upper panel) displays a series of original E waves, while the lower panel displays the same series with measured slopes. The "slope" function automatically provided the time duration of each slope (in milliseconds). Measurements were stored on a spreadsheet for further analysis. After analyzing all EWAA data, investigators (M.A.E., M.J., G.D.) excluded all echocardiographic studies which were perceived as technically poor. Reported results were agreed on by all investigators.

Interobserver variability was tested using both the Bland-Altman plot (linear regression revealed no trend between the mean and the difference, $P=0.9206$) and the inter-class correlation coefficient, resulting in excellent agreement between the measurements (0.87 [95% CI: 0.75-0.94]) [8].

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2) Area calculations: The area bounded between the slope (s) of the EWAA, the zero velocity line, and the vertical connecting the peak of the E wave with the zero velocity line was calculated for 1- and 2-slope EWAA. For a 1-slope EWAA, the area was calculated as the area of a triangle, where the height of the triangle was the calculated peak E wave (in cm/sec) and the base of the triangle was the duration of the slope (in sec) divided by 2. Peak E wave was calculated from the product of the measured slope (cm/sec²) and the duration of the slope (sec). In the case of a 2-slope EWAA, the area was calculated from the sum of the areas a, b, and c, as shown in **Figure 2**.

Demographic and clinical data

After summarizing the echocardiographic analysis, demographic and clinical data (age, gender, and risk factors) were collected from electronic medical records.

Final analyses and statistics

Analyses were performed per waves and per patients in a study group. For each group of subjects, the percentage of EWAA with 2 slopes was calculated. Values of the slopes and their respective durations were stored and compared between the groups. Sample sizes and power considerations: Preliminary observations indicated that the rate of 2-slope EWAA among random E waves was approximately 30%. Aiming to find a 15% difference between the HC and HFPEF groups, a sample size of 326 waves (163 in each group) was required for 80% power and 5% alpha (two-sided test). The final sample size included 199 waves in the HFPEF group and 166 in the HC group, increasing the statistical power to 84.5%. Statistical analysis: Categorical variables are presented with frequencies and percentages, while continuous variables are presented with mean, standard deviation (SD), median, and interquartile ranges. Association levels between the 3 study groups (HC, HFPEF-RF, and HFPEF) and categorical variables were examined using Chi-square tests (or Fishers' exact tests). For continuous variables, ANOVA (or Kruskal-Wallis test) was used. Pairwise comparisons (with Bonferroni's correction) were performed using Chi-square tests (or Fishers' exact tests) for categorical variables and t-tests (or Wilcoxon two sample tests) for continuous variables.

Statistical analyses were performed using SAS 9.4 software. $P < 0.05$ indicates statistical significance.

Results

Study population

A total of 183 subjects and 526 E waves were studied. The study groups, HC, HFPEF-RF, and HFPEF, included 57, 60, and 66 subjects, respectively. There were 166, 161, and 199 E waves available for analysis in HC, HFPEF-RF, and HFPEF groups, respectively. The HC group was younger than HFPEF-RF and HFPEF groups. **Table 1** presents demographic, clinical, and standard echocardiographic characteristics of the 3 study groups. Echocardiographic measures of the interventricular septum, posterior wall, and LV mass delineate geometric differences between the study groups.

Percentage of EWAA with 1- or 2-slopes

HC, HFPEF-RF, and HFPEF groups had on average 2.91 (SD=0.7; Median=3), 2.68 (SD=0.60; Median=3), and 3.02 (SD=0.64; Median=3) E wave signals per subject, respectively. The percentage of EWAA having 1- or 2-slopes in each of the groups is shown in **Figure 3**. Chi-square tests applied to the percentage of 2-slope EWAA revealed a statistically non-significant association between the presence of a 2-slope EWAA and the study groups ($P=0.22$), despite the observed trend.

For each subject, percentages of EWAA having 2 slopes were calculated. For example, if a subject had a total of 3 recorded EWAA and 2 of them had 2 slopes, then the percentage was 66%. In HC, HFPEF-RF, and HFPEF groups, mean and standard deviation percentages of subjects having a 2 slope EWAA were $38.0 \pm 40.9\%$, $39.7 \pm 43.4\%$, and $50.1 \pm 44.2\%$, respectively (Kruskal-Wallis $P=0.223$).

Value of EWAA slopes

Table 2 shows the mean values of 1- and 2-slope EWAA, according to study groups. Analysis was performed per wave. In the case of 1-slope EWAA, the value of the slope increased from HC to HFPEF patients. However, differences did not reach statistical significance. In the case of the 2-slope EWAA, values

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Table 2. Values of EWAA slopes (per wave analysis)

	HC	HFPEF-RF	HFPEF	p value
1-slope	1072.3±399.8 [981.0] (n=103)	1163.1±469.6 [1057.5] (n=98)	1227.3±509.8 [1091.0] (n=107)	0.089
2-slope Early s-EWAA	1616.1±703.2 [1556.0] (n=63)	1565.1±759.1 [1358.0] (n=63)	1736.1±644.7 [1650.0] (n=92)	0.1176
2-slope Late s-EWAA	517.4±476.1 [421.0] (n=63)	453.5±362.7 [382.0] (n=63)	452.8±228.6 [379.5] (n=92)	0.6011

Mean ± SD [Median]. Unit of slope value: cm/sec². Abbreviations as in text.

Table 3. Values of EWAA duration

	HC	HFPEF-RF	HFPEF	p value
1-slope Duration	74.4±23.0 [74.0] (n=103)	67.7±21.3 [65.5] (n=98)	73.9±20.7 [78.0] (n=107)	0.0365*
2-slope Duration of early s-EWAA	35.0±21.4 [28.0] (n=63)	36.7±23.5 [32.0] (n=63)	28.8±10.8 [28.0] (n=92)	0.120
2-slope Duration of late s-EWAA	53.9±16.7 [53.0] (n=63)	56.0±19.0 [53.0] (n=63)	58.7±15.7 [57.0] (n=92)	0.1318

Mean ± SD [Median]. Unit of slope duration: msec. *Pairwise comparisons revealed significant differences between HFPEF and HFPEF-RF (P=0.0165). Abbreviations as in text.

Table 4. Area bounded by the slopes of the EWAA and the zero velocity line (per wave analysis)

	HC	HFPEF-RF	HFPEF	p value
1-slope EWAA	2.72±1.01 [2.68] (n=103)	2.46±1.11 [2.33] (n=98)	3.20±1.44 [3.06] (n=107)	0.0005
2-slope EWAA	3.87±1.33 [3.74] (n=63)	4.06±1.23 [3.86] (n=63)	4.00±1.12 [4.14] (n=92)	0.2936

Abbreviations as in text. Unit of area is: cm. Pairwise comparisons for 1-slope EWAA revealed significant differences between HFPEF and HFPEF-RF (P=0.0002).

of the early s-EWAA in all 3 groups were greater than the values of the slope in the 1-slope EWAA, by approximately 34-50% (differences were statistically significant, P<0.001). The greatest value of the early s-EWAA was noted in the HFPEF group, followed by the HC group. The value of the late s-EWAA was greatest in the HC and smallest in the HFPEF group. However, differences did not reach statistical significance.

Duration of EWAA slope

Durations of the 1- and 2-slope EWAA were measured (Table 3). In the case of 1-slope EWAA, the duration of the slope was the smallest in HFPEF-RF, while the duration in both HC and HFPEF groups was similar. Differences between average slope duration in the HC and HFPEF groups were <1 msec. In the case of 2-slope EWAA, the early slope was shortest in duration in the HFPEF group. Yet, this did not reach statistical significance, differentiating the HFPEF group from other groups. The 2-slope EWAA in HC and HFPEF-RF shared similar durations, within a range of <3 milliseconds. Durations of the late s-EWAA were similar, within a range of 5 milliseconds, with no statistically significant differences between the groups. A trend was observed where the shortest late s-EWAA was observed in the HC group, increasing in HFPEF-RF, and further increasing in

HFPEF. The point of slope deflection, between early and late s-EWAA, occurred at 62.1%, 61.6%, and 66.9%, of the duration of the EWAA in the HC, HFPEF-RF, and HFPEF groups, respectively (differences were significant between HFPEF and HC, P=0.024, HFPEF and HFPEF-RF, P=0.015).

Area bounded by the slope of the EWAA

Table 4 shows the calculated area under the EWAA in the study groups, according to the slopes of EWAA (per wave analysis). In the case of a 1-slope EWAA, the area was smallest in HFPEF-RF and greatest in the HFPEF group. In the case of 2-slope EWAA, the areas were quite similar.

Discussion

The present retrospective descriptive study focused on the frequency of 2-slope EWAA in 3 groups, healthy controls, individuals with risk factors for HFPEF, and HFPEF patients. Main results: A) Prevalence of a 2-slope EWAA in HC, HFPEF-RF, and HFPEF groups was approximately 38%, 39%, and 46%, respectively (between group differences were not statistically significant, despite a trend); B) Slope measurements in all 3 groups showed significant differences between the value of the early s-EWAA (when

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2-slope EWAAAs were detected) and the value of the 1-slope EWAA; and C) The area bounded by the EWAA was always greater when 2 slopes were observed.

The prevalence of 2-slope EWAA was common (in all study groups). However, this could still be a subjective matter of eyeball examination and measurement error. Result B supports the hypothesis that 2-slope EWAA exists, since the values of 1-slope EWAA significantly differed from the values of the early s-EWAA when 2-slope EWAAAs were detected.

Mechanics of transferring blood from LA to LV during E wave ascending arm

In the case of a 1-slope EWAA, the sum of all pressures operating on blood volume multiplied by the area of the mitral valve is constant ($\Sigma P_i(t) \cdot MVA(t) = \text{constant}$ and t is the time duration of the EWAA). In the case of a 2-slope EWAA, a_1 and a_2 are defined as the observed early and late slopes of the EWAA, where $a_1 > a_2$. Accordingly, a_1 obligates $\Sigma P_i(t_1) \cdot MVA(t_1)$ to be constant during time interval t_1 . Similarly, a_2 obligates $\Sigma P_i(t_2) \cdot MVA(t_2)$ to be constant during time interval t_2 , where t_1 and t_2 are the time durations of the early and late EWAA slopes, respectively. This formulation clarifies that, during the EWAA, the product $\Sigma P_i(t) \cdot MVA(t)$ determines the value of s-EWAA.

MVA varies during EWAA, as shown in Figure 6A in the study by Bowman et al. [4]. At the onset of EWAA, MVA increases rapidly, reaching a peak prior to (by MRI measurement) or with (by echocardiography) peak E wave [4]. This means that, on average, MVA increases from EWAA onset to peak E wave. According to the formulation above, $\Sigma P_i(t)$ must decrease (proportionately to the increase in MVA) to maintain a 1-slope EWAA. Due to the mitral valve structure, it is accepted that MVA is determined by the operating atrio-ventricular pressures, $\Sigma P_i(t)$. Also, the faster blood flows between mitral leaflets, the lower the pressure between them. This decreases the effective MVA (Bernoulli effect). The interplay between $MVA(t)$ and $\Sigma P_i(t)$ determines blood acceleration and slope.

Physiological pressures operating on blood during E wave ascending arm

During EWAA, pressure propelling blood across the mitral valve originates in the LA, LV, right

heart, and chest (respiratory variation of intrathoracic pressure and pericardium). The passive pressure gradient between LA and LV is affected by: A) The beat-to-beat variation of blood volume flowing from the lungs to the LA [9]; B) LA compliance; and C) The pressure within the LV when the mitral valve opens, assuming LV diastolic suction is absent. Passive (LA-LV) PG determines the initial conditions for blood flow. However, it does not predict the 2-slope EWAA phenomenon. Mitral valve opens and MVA increases, $\Sigma P_i(t)$ must decrease in response and the bilateral interaction described above occurs. Assuming this scenario, a blood driving force is neither added nor removed. The passive initial (LA-LV) PG decreases because of the transfer of blood from LA to LV. Therefore, it is predicted that the value of a 1-slope EWAA would vary according to a beat-to-beat dependent set of initial pressure conditions [9].

Elastic recoil and diastolic suction added to the passive (LA-LV) PG creates a possible blood driving force [7], [10-16]. Elastic recoil acts to further rapidly decrease LV pressure relative to LA pressure, thereby increasing the gradient (LA-LV) PG. Bell and colleagues described that most of the elastic recoil terminates before mitral valve opening [7]. If this force decays during EWAA, it will induce a change in $\Sigma P_i(t)$, creating a change in the EWAA slope. Thus, the presence of elastic recoil and its timely decay during the EWAA may explain a 2-slope EWAA. Mechanical forces derived from the right heart and pericardium may also affect the LA pressure build up just before mitral valve opening, as well as during early diastole (as in the case of cardiac tamponade [17, 18]). A "preferred" filling of the right ventricle during inspiration causes the septum to deviate towards the LV, exerting a force opposing trans-mitral flow. Theoretically, this can occur during the early diastolic filling phase and cause a change in EWAA slope. Yet, none of the subjects of this study experienced cardiac tamponade. An increase in intrathoracic pressure related to the breathing cycle (e.g., expiration decreasing venous return), accidentally occurring during EWAA, causes the volume of blood arriving at the LA to decrease. This may decrease $\Sigma P_i(t)$ during EWAA, potentially creating the 2-slope EWAA phenomenon. If this were the mechanism, it would be expected that in approximately half of the sampled E waves where 2-slope EWAA was present, an increase rather than a

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decrease in the late EWAA slope would be observed (due to a decrease in intrathoracic pressure during inspiration increasing venous return).

Finally, Doppler wave measurements were determined in 2D at the level of mitral leaflets. Blood mass flows through this point. However, the angle between the direction of blood flow and the Doppler signal source varies during early diastole due to untwisting motion of the LV. Such a change in angle affects measured blood velocity. This may explain the prevalence of 2-slope EWAA observed in HC and HFPEF-RF groups. In conclusion, 2 slope-EWAA may be explained by a change in a blood driving force occurring during the EWAA or a change in the angle between the Doppler source and the direction of blood flow or both. A change in the MVA during EWAA that produces a change in s-EWAA is less likely to explain the 2-slope EWAA phenomenon. First, according to magnetic resonance imaging [4], MVA increases linearly up to the peak of the E wave. Second, it is assumed that $MVA(t)$ follows $\Sigma Pi(t)$ at the beginning of diastole, as the mitral valve opens. Third, due to Bernoulli effects on mitral leaflets, MVA decreases at some time t_k during the EWAA. Thus, $\Sigma Pi(t)$ will change its rate of decrease at time t_k as well. This scenario is predicted based on the mutual effects of $MVA(t)$ and $\Sigma Pi(t)$. This scenario preserves a constant product $\Sigma Pi(t) \cdot MVA(t)$, leading to constant acceleration.

HFPEF and the 2-slope EWAA phenomenon

Results demonstrated a trend where 2-slope EWAA was more prevalent in the HFPEF group, compared to either HFPEF-RF or HC groups. The area below a 2-slope EWAA was always greater than that below a 1-slope EWAA. As the area under the EWAA reflects the amount of blood passing from LA to LV during the EWAA, it is clear that more blood is transferred with a 2-slope EWAA (compared to 1-slope EWAA). Therefore, it is possible that, to compensate for a decreased late diastolic LV filling occurring in HFPEF (due to the concentric hypertrophy remodeling process rendering the LV non-compliant), a shift occurs from 1-slope to 2-slope EWAA. This scenario is concordant with the shift in E/A ratio observed as diastolic dysfunction progresses [19]. A canine model revealed

that restoring forces (and thus diastolic suction) increased as a function of the difference between end systolic volume and the slack or equilibrium volume [7]. The latter is a unique LV volume where transmural pressure equals zero. Greater differences led to greater restoring force [7]. In a meta-analysis, ejection fraction in HFPEF patients, a measure of systolic function, was shown to be slightly greater than that in HC [20]. It is possible (though not proven) that a greater systolic contraction leads to a smaller end systolic volume and a greater volume difference from the slack volume. Accordingly, this scenario may favor recruitment of elastic recoil as a mechanism for maximizing early LV filling. If the termination of elastic recoil during EWAA underlies the change in s-EWAA, accounting for the 2-slope EWAA phenomenon, then why is this mechanism recruited intermittently (the phenomenon was demonstrated in only half of the E waves)? It is possible that elastic recoil is recruited in every diastole. However, the time of termination of elastic recoil may occur either before or after EWAA. In such cases, a change in $\Sigma Pi(t)$ will not be visible during EWAA. This theoretic explanation may hold for the 2-slope EWAA phenomenon observed in HC.

The present retrospective study analyzed EWAA data acquired by several echocardiographic technicians that were not part of this study, with no special attention to the acquisition of diastolic transmitral flow velocity waves. Therefore, the data set reflects "real world" trans-mitral flow velocity data. However, it imposes limitations, such as a limited amount of EWAA per patient. The latter precludes studying the pattern of occurrence of 2-slope EWAA in a longer series of EWAA. When observing 3 EWAA on a single screen, a bias may occur towards detecting a second EWAA with two slopes when a first one was observed. If a 1-slope EWAA was previously detected it could discourage investigators from detecting a 2-slope EWAA. These limitations could account for some over- or under-detection of the 2-slope EWAA phenomenon, but would not account for the between group differences. Study groups were classified according to clinical documentation and the presence of ejection fraction $\geq 50\%$. This classification is less rigorous than prospectively required [1], potentially including other medical conditions in the HFPEF group. Investigators acknowledge that they were

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biased towards detecting 2-slope EWAA, as this phenomenon was the subject of the study. This bias probably led to a higher rate of detection of the 2-slope EWAA in all three study groups. However, the different trend in the rate of the phenomenon is accepted as true, as investigators were blinded to the association between clinical groups and echocardiographic signals.

Conclusion

In the present study, slopes of EWAA were studied, indicating that a 2-slope EWAA was prevalent in all study groups (HC, HFPEF-RF, and HFPEF). The underlying mechanisms were not clear. However, they may be related to an intrinsic cardiac effort to shift from late to early LV filling. If this is true, medications that induce negative inotropic and lusitropic effects, such as beta-blockers, may actually inhibit compensating physiological mechanisms.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Guy Dori, Internal Medicine E, Emek Medical Center, 21 Rabin Blvd. Afula 1834111, Israel. Tel: +972-50-6265516; +972-4-649-5050; Fax: +972-4-6495375; E-mail: guydori2512@gmail.com; guydo@clalit.org.il

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