

What Do You Want From Your Echocardiogram?

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Getting old can be tough. Cataracts form, joints deteriorate, arteries stiffen, and bone demineralizes. The heart is certainly not immune to senescence. Diastolic function shows perhaps the greatest deterioration: ventricular compliance decreases, and diastolic relaxation becomes prolonged.^{1,2} Heart rate and contractility no longer increase as they should when the heart is called on to pump more vigorously.³ When these changes become significant enough, it leads to the clinical syndrome of heart failure (HF) with preserved ejection fraction (HFpEF), the dominant cause of HF in elderly individuals and the quintessential expression of cardiovascular senescence.^{4,5}

Echocardiography is by far the most commonly used tool to evaluate for diastolic dysfunction (DD). Although certainly not perfect, tissue and Doppler echocardiography enables assessment of ventricular structure, function, and hemodynamics that is helpful diagnostically and prognostically.^{6–9} Because DD increases with aging, it has been suggested that we may need to account for this in what we consider to be “normal.” Shah and colleagues have recently proposed new age-based cutoffs that better predicted incident cardiovascular disease outcomes.¹⁰ However, the cutoff values that they proposed were derived from only 401 individuals, and more information is needed.

In this issue of the *Journal of the American Heart Association (JAHA)*, Naylor et al present important new data from the FHS (Framingham Heart Study) to help address this issue.¹¹ The authors examined a healthy reference sample of 2355 participants (mean age, 44 years) without prevalent cardiovascular disease or risk factors. Three echocardiographic variables of diastolic function were analyzed: tissue

Doppler lateral mitral annular e' velocity, the E/e' ratio, and the E/A ratio. Abnormal values were defined by the outer 10th percentile from the healthy cohort, separated by decade of life and sex. These cutoffs were then applied to the broader FHS sample of 6102 subjects.

Age was the strongest correlate of DD when using a single cut point to define abnormal (not accounting for age or sex), most notably in those with “mild” DD (defined as any 1 of 3 criteria abnormal).¹¹ More than 65% of subjects aged ≥ 80 years had some element of DD by current single cut point criteria. However, after applying the age- and sex-specific criteria, only 15% to 22% of the sample had mild DD and 10% had moderate or severe DD (defined as 2 or 3 criteria abnormal), and the striking age dependence of DD vanished. In fact, although age was the dominant correlate of DD using the single cut point criteria, it became inversely correlated with DD in the fully adjusted model using age- and sex-specific criteria.

Using age- and sex-specific criteria, mild and moderate-severe DD were associated with 50% and 65%, respectively, greater hazards of cardiovascular disease events, although this association was no longer significant after adjusting for other cardiovascular risk factors.¹¹ In contrast, using the single cut point criteria, mild DD was no longer predictive, but moderate-severe DD remained similarly predictive of events. Naylor and colleagues are astute in that they do not conclude from their data that age- and sex-specific reference limits *should* be used to assess DD, but they rather point out some of the tradeoffs that must be considered by clinicians and investigators, which will require additional study moving forward.¹¹

The authors are to be commended on this important contribution to the literature.¹¹ The large, well-characterized, community-based sample, the systematic prospective acquisition of data, and the careful adjudication of events are all major strengths. Like all studies, there are some limitations to consider. For the reference population, the authors were careful to exclude participants with prevalent cardiovascular disease and important risk factors for DD, like obesity, but other factors, such as physical activity and fitness, were not accounted for, and these may strongly affect diastolic function and risk of HFpEF.^{12,13} One could make a cogent argument that the reference sample should include individuals

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who are both active and fit to represent the ideal of “successful” cardiac aging.^{12,14} Incident HF events were infrequent, and so a composite cardiovascular outcome that included myocardial infarction, stroke, and claudication was used by the authors.¹¹ The study was not adequately powered to assess for HF-specific end points.

Despite these limitations, the data from Naylor et al¹¹ provide valuable new insight into cardiac aging while raising questions about how we should define DD across the age spectrum using echocardiography. The velocity of left ventricular diastolic annular motion during early diastole (e') decreased strikingly with age, by 9% in men and 12% in women per decade. Shah et al also recently observed a precipitous decline in e' velocity with aging, although the derived cutoff values from their study and the current study to define “abnormal” were different (Table).^{10,11} Further study is required to resolve these discrepancies. The E/e' ratio, a surrogate for left ventricular filling pressures,^{6,9} increased with aging, and the slope of this increase appeared to be steeper in women (Table), consistent with published data from other cohorts.¹ This is noteworthy when considering how women are more likely to develop HFpEF than men with aging.¹⁵ In both studies, the age- and sex-specific cut points for E/e' did not differ as greatly from the guideline-based cutoff as e' velocity did.^{10,11}

Although age-specific cutoffs may provide greater insight into prognosis, at least for mild DD,¹¹ one unintended consequence of incorporating these criteria into practice could become a tacit acceptance that any DD is normal. There is no question that the prevalence of DD increases with age, but that does not diminish the fact that DD is harmful. Mild DD in elderly individuals at rest generally does not reflect high filling

pressures,¹⁶ but what is mild at rest may become profoundly limiting during stress in the setting of HFpEF, where the inability of the ventricle to enhance e' velocity leads to marked elevation in cardiac filling pressures.¹⁷ High filling pressures lead to symptoms of dyspnea and impairments in functional capacity,^{18,19} which may perpetuate sedentary behavior and reduce quality of life. These end points are sometimes more difficult to measure and were not evaluated in the current study, but they can be important to our patients.

The data from Naylor and colleagues show that risk prediction for “hard end points” is improved with age-specific diastolic indexes,¹¹ but this may incur a cost that we also need to contemplate (Figure). Liberalizing the cutoffs for what is considered normal diastolic function in older adults could worsen the existing problem of underrecognition of HFpEF in people with dyspnea, especially when one considers that the echocardiographic assessments currently in use are poorly sensitive.⁶ Use of age-specific criteria may also promote tacit acceptance that DD (when associated with aging) is benign, which is not the case, at least for the symptomatic expression of cardiac insufficiency.^{5,17,19} This could deepen the nihilistic perception that seniors with dyspnea (often attributable to HFpEF) are “just getting old,” rather than experiencing objective limitations in cardiac function.

As shown by Naylor et al in their Figure 1B, the prevalence of DD increases strikingly with age using single cut point criteria.¹¹ This perfectly mirrors what we see plotting the prevalence of HFpEF as a function of age.⁴ However, using the age- and sex-specific cutoffs, the prevalence of DD remains stable across the lifespan and is much lower in seniors (Figure 1A).¹¹ This is incongruent with what we know about

Table. Age, Sex, and Echocardiographic-Doppler Indexes of Diastolic Function

Variable	Mean Value in a 40-Year-Old Adult Without CVD*	Estimated Change per Decade of Life in an Adult Without CVD [†]	Relative Change per Decade of Life Without CVD, %	Partition Value for Abnormal in FHS for Age >60 y [‡]	Partition Value for Abnormal in ARIC Study for Age >65 y [§]
Lateral E' velocity, cm/s					
Women	13.0	−1.5	−12	<7.7	<5.1
Men	13.1	−1.2	−9	<8.1	<5.4
Lateral E/e' ratio					
Women	4.7	+0.4	+9	>9.0	>13.3
Men	5.2	+0.2	+4	>7.4	>11.5
E/A ratio					
Women	1.5	−0.2	−13	<0.8	NA
Men	1.5	−0.2	−13	<0.7	NA

A indicates late diastolic mitral inflow velocity with atrial contraction by pulsed wave Doppler; ARIC, Atherosclerosis Risk in Communities; CVD, cardiovascular disease; E, early diastolic mitral inflow velocity by pulsed wave Doppler; e' , early diastolic mitral annular velocity by tissue Doppler; FHS, Framingham Heart Study.

*Estimated from Y value at age 40 years in the mean regression lines from Supplemental Figures 2 through 4 from Naylor et al.¹¹

[†]Estimated from the slope of the mean regression lines from Supplemental Figures 2 through 4 from Naylor et al.¹¹

[‡]Weighted means based on age distribution from Naylor et al.¹¹

[§]Taken from Shah et al.¹⁰

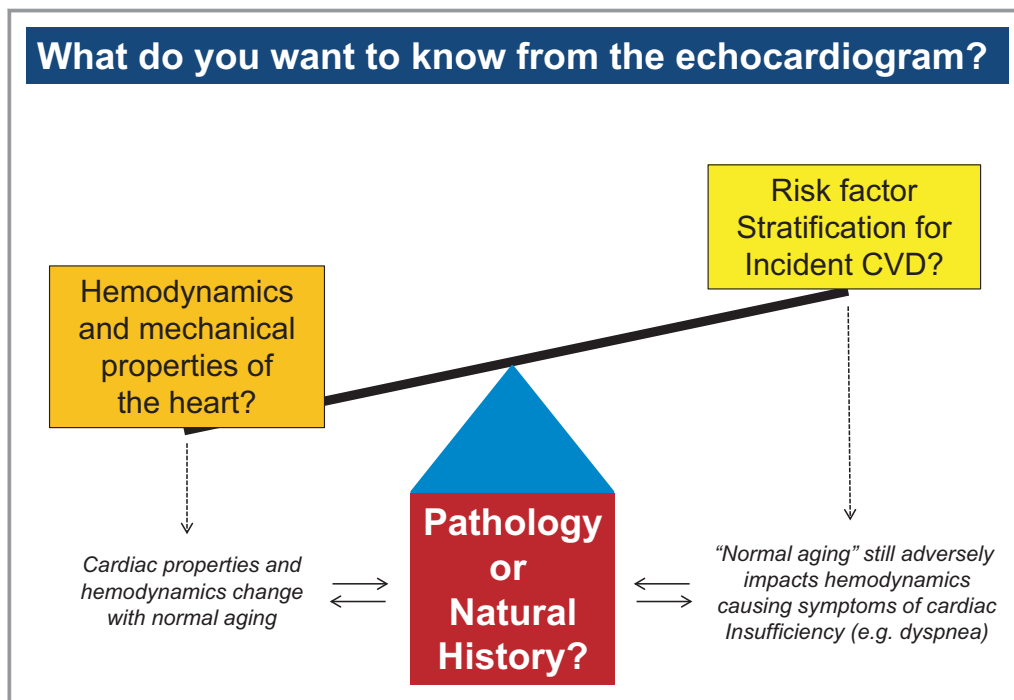


Figure. Tradeoffs between considering left ventricular diastolic function in absolute terms as normal or abnormal, or relative to what is seen during normal aging. See text for details. CVD indicates cardiovascular disease.

cardiac aging,¹ and it would seem inappropriate to label diastolic function as normal when it clearly is not.

It might be helpful to reflect on lessons from the past when considering this dilemma. For years, we thought that “essential” hypertension was an inevitable consequence of aging that was necessary to maintain organ perfusion in older adults, which therefore did not require treatment. Epidemiologic studies including the FHS and then clinical trials eventually proved that is not the case. Why should age-related DD be any different? Age is typically considered to be an unmodifiable risk factor, but recent studies have shown that interventions, such as exercise training^{12,14} or weight loss,²⁰ can reverse or at least mitigate age-related DD. Even the cellular mechanisms of cardiac aging might one day become treatable.²¹

There is no question that DD becomes more common as our hearts age.^{1–3} That does not mean that we should just accept it or call it normal. When ventricular compliance decreases and relaxation becomes prolonged, the pressure in the left atrium goes up.⁵ This favors fluid redistribution out of the pulmonary capillaries and into the lung interstitium to cause congestion and dyspnea.¹⁹ This sequence of events plays out similarly in people in the third or the ninth decade of life. The lens through which we interpret diastolic data across the lifespan may differ for the epidemiologist, the physiologist, and the clinician. The question we need to ask ourselves is which perspective is best? The answer might be: a little bit of each.

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Disclosures

None.

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