arterial $^{18}$NaF signal was increased at levels similar to those for cortical bone. In the right femoral artery, the $cSUV_{\text{max}}$ was 0.2, 0.2, 2.1, and 1.1, and the TBR was 1.4, 1.3, 3.3, and 1.9; in the left femoral artery, the $cSUV_{\text{max}}$ was 0.2, 0.1, 2.2, and 1.3; and the TBR was 1.5, 1.1, 3.4, and 2.1 for the 4 patients with increasing age, respectively. On CT, the HU value in the lumbar vertebra 1 was 252, 169, 82, and 122, respectively. Values <120 are considered osteoporosis. Regarding the skin, patient 1 had severe skin abnormalities, both clinically and on PET, patient 2 had mild skin abnormalities both clinically and on PET, patient 3 had moderate skin abnormalities clinically and on PET, and patient 4 had moderate skin abnormalities clinically and severe on PET. Skin abnormalities were identified at all locations, and the severity and location of PET scores corresponded favorably with the clinical classification ($R_{\text{spearman}} = 0.44$, $p = 0.09$).

In conclusion, this is the first report showing that $^{18}$NaF PET/CT is able to visualize and quantify ectopic calcifications and bone metabolism in PXE and may prove a valuable intermediate mechanistic endpoint for therapeutic studies aiming to slow or remove MAC.

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Heart Rate Is an Important Consideration for Cardiac Imaging of Diastolic Function

We read with considerable interest the state-of-the-art paper, “Cardiac Imaging to Evaluate Left Ventricular Diastolic Function,” by Flachskampf et al. (1). The authors provide comprehensive coverage of the methods used to image and analyze diastolic function.

For 2 reasons, heart rate merits further discussion. 1) There is significant translational interest in diastolic function. It is sometimes underappreciated that, in the mouse and rat models, one cannot separate early diastolic and late atrial filling without significantly reducing the heart rate. 2) In humans, it is not possible to separate early diastolic and late atrial filling modestly at fast heart rates (>100 beats/min).

Figure 1A shows the importance of heart rate. Systolic duration was reduced only modestly, and E-wave peak velocity and timing were essentially unchanged as the heart rate increased. Atrial filling merges (fusion) with the E-wave until it was impossible to differentiate. The atrial contribution to filling is nearly preserved, simply adding to the E-wave (2).
Importantly, one cannot accurately quantify diastolic function without knowing what happens when the E-wave and A-wave are separated. The same principles apply to diastolic function in a mouse (3).

Figure 1B schematically shows an important caution: one might mistake the merged E-wave and A-wave as a restrictive filling E-wave and attribute other velocity features in the Doppler signal as the A-wave. This overestimates E-wave velocities and underestimates the deceleration time. Unfortunately, the example of restrictive filling in the review of Flachskampf et al. (1) (Figure 4 in their article) may be influenced by this issue. The systolic duration would be quite short (<200 ms) if the bright spot after the E-wave is truly the A-wave. If we assume that the QRS timing is accurately aligned with end-diastole, a more reasonable systolic duration (300 ms) is revealed between the fused E-wave and A-wave. This is consistent with the QRS timing to e' duration on the tissue Doppler image (TDI). But what is that bright Doppler velocity, if it is not the A-wave? The velocity is coincident with the S-wave of the TDI and is likely the result of the velocity of the blood and mitral valve toward the apex (4).

The authors appropriately note that analysis should be performed after the heart rate decreases if fusion occurs (1), and this point must be emphasized. Clinically, the E wave and e' velocities do not change much after the termination of exercise, so unmerged velocities should be obtained during the early recovery period (5).

The example presented in Figure 1 can help guide analysis of diastolic function and identify fusion of the E-wave and A-wave. Sonographers should be aware of the impact of a high heart rate, be able to identify it visually and quantitatively, and attempt to temporarily reduce it (an unfortunately difficult challenge in a rodent!). We urge investigators and clinicians to carefully consider heart rate in their evaluation of diastolic function.

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THE AUTHORS REPLY:

We thank Drs. Chung and Afonso for their interest and careful scrutiny of our article (1). We fully agree that heart rate and the fusion of the transmitral diastolic E-wave and A-wave occurring at higher heart rates are an important concern in assessing left ventricular diastolic function and find the example in Figure 1A of their letter, in particular regarding the shortened apparent deceleration time of the fused E-A signal. The authors raise the possibility that E-A fusion is present in our example of restrictive transmitral filling (Figure 4 [1]). This example is from a 40-year-old patient with uncontrolled hypertension, severe heart failure with pulmonary congestion, and a left ventricular ejection fraction of 30%. In general, at a heart rate of 100 beats/min, there may be E-A fusion. In our case, however, this would imply that the fused A-wave would occur before the end of the P-wave (Figure 1A, dashed blue line in the magnified beat from our original recording), which seems unlikely. We agree that the bright small wave well after the QRS duration is probably not the A-wave, but a small A-wave is visible immediately after the P-wave in the magnified beat (red arrow). We present an additional recording (Figure 1B) from this patient 3 days earlier than the that reproduced in our article, at a heart rate of 92 beats/min, again with a restrictive transmitral pattern, where the A-wave in beats 2 and 5 is well recognizable and the E-wave deceleration time is 95 ms, similar to the deceleration time of 102 ms in Figure 4 in our paper (1). In the other beats in Figure 1A, the A-wave is less well defined, but definitely not merged with the peak of the E-wave.

![Figure 1](image_url)

**Figure 1** Restrictive Transmitral Pulsed-Wave Doppler Profile

(A) fourth beat from Figure 4 in our article (1). The E-wave ends before the end of the electrocardiographic P-wave (blue lines), making E-A fusion unlikely. There is a small wave (red arrow) immediately after the E-wave and the electrocardiographic P-wave, which is probably the real A-wave. (B) Transmitral profile of the patient in Figure 4 in our paper (1), obtained 48 h earlier at a slightly lower heart rate (92 beats/min). A clear A-wave is visible in beats 2 and 5. The E-wave deceleration time is 95 ms, similar to the deceleration time in Figure 4 of our paper. Peak E-wave velocity in both figures is ~100 cm/s. bpm – beats per minute.