Should we be on the fence or can we open the gate? Evidence that QRS gating in FMD analysis is not essential

K. E. Pyke
Cardiovascular Stress Response Laboratory, School of Kinesiology and Health Studies, Kingston, Ontario, Canada

The function of arterial endothelial cells is now recognized as an important factor in the pathogenesis of atherosclerosis. Almost two decades ago, Celermajer and colleagues (2) introduced a noninvasive assessment technique to evaluate endothelial function in humans. In this test, the magnitude of conduit artery endothelial-dependent vasodilation that occurs in response to a blood flow-associated increase in shear stress is taken as the index of endothelial function [flow-mediated dilation (FMD)]. Shear stress is increased via the release of temporary limb occlusion (reactive hyperemia). Since its introduction, the possibility of refining “the FMD test” for clinical application has been revisited frequently, and efforts continue to optimize its utility as a research tool. This has driven the field toward a progressively more rigorous definition of what is considered “best practice” (4, 7, 11). This process has occurred alongside rapid technological advancement, and it is thus not surprising that diameter analysis techniques for FMD assessment have evolved considerably since the early 1990s.

Initially diameter assessment was dominated by manual electronic caliper measurements from B-mode ultrasound images taken at baseline and at discrete time points during hyperemia (2, 5, 9). This labor intensive technique permitted few measurements and the timing of each was aligned with end-diastole, taken as coincident with the onset of the QRS complex (“QRS gating”; 2, 5). Moderated by the degree of arterial stiffness, arterial diameter changes as a result of changes in pressure that occur over the cardiac cycle. Clearly, if baseline and peak diameter measurements were taken by caliper placement at distinct phases of the cardiac cycle, the across-cycle fluctuation in diameter would influence the FMD assessment (3; Fig. 1). QRS gating prevents a contribution of cardiac cycle-induced diameter change, allowing isolation of shear stress-stimulated changes. Manual caliper assessment is now used less frequently as automated edge detection software becomes increasingly available. Several different versions have been developed and are used by different groups (10, 12, 13). Edge detection software allows users to select a region of interest (ROI) on the image and can output a diameter measurement within that ROI for each frame in the image clip. Edge detection software validated against phantom arteries has been shown to reduce intraobserver variability of both baseline diameter and calculated %FMD measurements vs. the manual caliper procedure (14). In addition, due to the vastly increased number of diameter assessments (1 per frame) software permits continuous measurements over the entire cardiac cycle and FMD protocol. Depending on compatibility with the ultrasound system, the diameter analysis software may or may not be able to automatically select images that are gated to the QRS complex.

Published FMD guidelines strongly recommend QRS gating (4, 7), thus including gating as a part of the best practice.
definition. Indeed, in the most recent recommendations it is indicated that the diameter change across the cardiac cycle “may be as much as 1 mm, which if unaccounted for, may completely confound the assessment of FMD” (7). Reviewers look to published guidelines when evaluating methodology. Such a definitive recommendation, with such dire stated consequences if not followed, could come to be used as grounds for rejecting manuscripts for publication. Notably this strong recommendation is not supported by references comparing FMD measurements taken only at end diastole vs. those taken continuously (Fig. 1). Interestingly, and in conflict with this recent QRS gating recommendation, some groups with considerable experience in FMD research have moved away from gating, citing relatively small sample size (10) or unpublished observations (1) of a lack of difference between gated and continuous diameter assessment.

In this issue of the Journal of Applied Physiology, Kizhakekuttu and colleagues (8) provide the first systematic investigation of the necessity of QRS gating in the assessment of FMD and nonendothelial-dependent dilation stimulated with sublingual nitroglycerin (NMD). Importantly, they performed this analysis in subjects with a range of brachial artery distensibility, (young, healthy older, and type 2 diabetic subjects). Thus they studied a population that could be expected to have variability in cardiac cycle-induced diameter changes associated with the range of arterial stiffness. This allowed them to address the concern that differences in arterial stiffness would influence FMD calculated from continuous diameter measurements. They found that neither FMD nor NMD differed significantly when measured via QRS gated diameters or diameters taken as an average over the whole cardiac cycle. Indeed, in Bland-Altman plots, bias approached zero, and differences in calculated FMD between the two methods were <2% with few exceptions. This suggests that either gated or un gated analysis is acceptable. Kizhakekuttu and colleagues (8) point out that their system was not able to automatically select images gated to the electrocardiogram (ECG) trace, instead requiring manual selection of the diameter at end diastole, significantly increasing analysis time. Thus, depending on the system, QRS gating may add both difficulty and cost to analysis—certainly only desirable if it improves the quality of measurement. Importantly, this data challenges current guidelines and underscores the importance of performing systematic investigations to avoid enforcement of potentially unnecessarily restrictive recommendations.

Are we still on the fence? Certainly we may still ask the question, could QRS gating in FMD test analysis still be important? The findings of Kizhakekuttu and colleagues (8) are supported by those of Padilla and colleagues (10) and Gemignani and colleagues (6) who employed a filter to eliminate the cardiac cycle-induced diameter changes and compared this to end diastolic measurements. However, further studies that investigate the impact of gating in subjects with a greater range of distensibility, and with diameter measurements over the whole hyperemic period, rather than during discrete time intervals (as was done by Kizhakekuttu et al., 8) would be helpful. With respect to the latter, there is a wide range in time to peak diameter, which can differ significantly between populations. Diameter assessment at discrete time points or intervals during hyperemia can therefore miss the true peak FMD (1).

In summary, the data reported by Kizhakekuttu and colleagues (8) strongly suggests that QRS gating to isolate end diastolic diameters for FMD assessment does not yield a significantly different assessment of FMD vs. diameters that are averaged over the whole cardiac cycle. Importantly this is in contrast with current technical guidelines that strongly advocate the use of end diastolic diameters and suggests instead that QRS gated or continuous diameter measurements may be equally appropriate for FMD assessment.

REFERENCES