this group may indeed be related to intrinsic changes in heart rate. The same cannot be true for the ASF lineman. This subgroup of athletes had no change in resting heart rate, an indirect marker of unchanged cardiorespiratory fitness, and developed relative hypertension and concentric LV hypertrophy. Thus, the observed reductions in LV longitudinal strain are in no way analogous to the myocardial mechanics we and others have described among endurance athletes but are more consistent with early-stage hypertensive remodeling. Second, there were several issues regarding our statistical analyses, including variable selection and the number of independent variables used in our regression modeling. Regarding variable selection, specifically the potential for high collinearity, it is important to consider the heterogeneous nature of the study cohort. ASF populations comprise athletes spanning the full spectrums of body size, sport physiology, and LV remodeling, making collinearity less of an issue than it would be in a more homogenous study population. While opinions regarding the appropriate number of independent variables for use in a multivariate analysis differ, we chose a standard and rather conventional approach in which we limited variable inclusion to no more than 1 per 10 subjects. Finally, potential mechanisms underlying higher heart rates among linemen versus nonlinemen are considered. We concur that ASF linemen may very well have an autonomic balance favoring sympathetic over parasympathetic activity, particularly in comparison to nonlinemen, but think it is unlikely that this is driven by a deprived parasympathetic nervous system. The statement that "linemen are exposed to high-volume endurance training during the season, but have still the same or even higher heart rates than other players do" is inaccurate, and we encourage Tadic and colleagues to rethink field position–specific physiology underlying the ASF participation. In reality, linemen get very little endurance training but rather engage repetitively in activities characterized by nearly pure isometric physiology. In addition, ASF linemen often concomitantly gain weight, eat high-sodium diets, use high quantities of nonsteroidal anti-inflammatories, and experience increases in resting blood pressure. One need not complicate the pathophysiologic picture by invoking intrinsic deficiencies in autonomic nervous system function when these simple physiological explanations are such low-hanging fruit.

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FFR-Derived From Coronary CT Angiography Using Workstation-Based Approaches

Computed tomography (CT) angiography–derived fractional flow reserve (FFR) is a potentially disruptive technology in its ability to noninvasively predict coronary FFR values. Promising initial results have engendered vigorous discussions about this particular image analysis pathway as a gatekeeper to the catheterization laboratory. There is evidence to suggest that CT-derived FFR can significantly improve the detection of obstructive coronary artery disease (CAD) and avoid unnecessary invasive testing, with beneficial economic and quality-of-life outcomes.

Hence, we have read the article by Ko et al. (1) with great interest. As discussed by the authors, one major limitation of the currently commercialized, Food and Drug Administration–approved solution for CT-based FFR derivation consists in the need for transferring patient image data to an external core laboratory. The calculation and transfer process remains time consuming (around 1 to 4 h) and is less suitable for prompt clinical decision making, which obviously limits the practical utility. As a result, less computationally demanding approaches residing on a regular workstation have been developed and implemented, involving, for instance, reduced-order computational

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fluid dynamics and artificial intelligence deep-machine learning. Ko et al. (1) present the technical principles and general feasibility of yet another novel CT-based FFR prototype based on structural and fluid analysis to determine the physiological significance of coronary lesions. Compared with conventional coronary computed tomography angiography (CTA), the novel approach enabled a marked improvement in specificity (87% vs. 74%) and positive predictive value (74% vs. 60%), while the traditionally high sensitivity and negative predictive value of coronary CTA were preserved. The novel approach was reported to require short processing time (30 min) using a standard desktop computer.

We agree with the authors that the development of physician-driven, workstation-based analysis methods may be one of the necessary next steps to implement CT-derived FFR as a routine clinical test. In addition, we would like to direct the readers to additional studies using fast on-site algorithms. Our own laboratory investigated a different approach for workstation-based analysis using reduced-order computational fluid dynamics and recorded a mean duration of 37.5 ± 13.8 min for CT-FFR derivation including data pre-processing and coronary blood flow computation. In 67 lesions a significant improvement in specificity (85% vs. 34%) and positive predictive value (71% vs. 37%) was accomplished in comparison with coronary CTA alone (2). Using the same application, Kruk et al. (3) focused on the evaluation of patients with intermediate lesions (50% to 90%) and concluded that in approximately one-half of the patients CT-FFR allows for discrimination between ischemic and nonischemic stenoses.

Further, the performance of artificial intelligence deep-machine learning CT-FFR-derivation (4) is currently being evaluated by the MACHINE (Machine leArning Based CT angiograpHy derIved FFR: a MulticeNtEr registry) consortium (NCT02805621). With an estimated population of 352 patients from 5 centers we aim to investigate the comparative performance of computational fluid dynamic modeling and machine learning approaches for determining the functional significance of coronary artery stenosis validated against invasive FFR measurement.

What all these newer developments, including the one currently reported on by Ko et al. (1), have in common is their on-site, workstation-based, physician-driven availability. Besides arguably being better suited for routine clinical workflows, the integration of CT-FFR algorithms into a workstation environment also has potential to broaden the current focus on a single number (i.e., the FFR value) for guiding ad hoc patient management to a more comprehensive exploitation of the considerable richness of coronary CTA data. Our current workstations feature a broad spectrum of advanced, sophisticated tools for characterizing and quantifying the extent of atherosclerotic disease, features that have shown surprisingly powerful prognostic value in many investigations, most recently by harnessing our rapidly evolving machine learning capabilities (5). Integrating the ability of noninvasively determining lesion-specific ischemia with these powerful risk prediction and stratification methods may prove to be a readily available truth machine at our fingertips to determine which patient needs our help right now and in future.

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THE AUTHORS REPLY:

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