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EDITORIAL COMMENT

The Many Dimensions of Diastolic Function

A Curse or a Blessing?*

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Left ventricular filling involves a number of physiological processes, including untwist (which generates suction), myocardial relaxation, and left ventricular compliance. Each of these processes may be disturbed by a variety of causes, including aging, degenerative changes, myocardial energetics, and fibrosis. Moreover, each process is also manifested by numerous signals that can be measured using imaging techniques varying from untwist to isovolumic relaxation, the balance between passive and active left ventricular filling, relaxation velocity, and so on. Perhaps because of the heterogeneous contributors to these signals, the development of multiple echocardiographic parameters has challenged the clinician's ability to interpret diastolic function. Repeated updates in algorithms have sought to bring together multiple parameters in an empirical approach, but the concordance of observers with previous iterations of the recommendations for assessing diastolic dysfunction has been limited (1), and the validity of the approach presented in the current recommendations (2) is a matter of ongoing investigation.

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In this context, modern statistical approaches for separating, classifying, and visualizing patient-centric models could greatly facilitate the meaningful integration of routinely acquired echocardiographic parameters. To this end, Selmeryd et al. (3), in this issue of *iJACC,* describe the development of a multivariable statistical model using novel computational approaches that combine age-related changes in diastolic variables for differentiating normal from abnormal filling patterns.

Selmeryd et al. (3) used a derivation cohort of 1,240 visibly healthy subjects from the Nord-Trøndelag Health Study. These investigators developed a polynomial regression model of transmitral filling in which peak early and late diastolic transmitral filling velocities (E and A) and early diastolic mitral annular velocity (e′) were combined as a function of age. Just as *z*-scores indicate how many SDs an observation is from the mean and provide a dimensionless quantity, Selmeryd et al. (3) used a dimensionless distance metric (Mahalanobis distance, which provides a multivariable generalization of a *z*-score) for developing a multivariable reference range for transmitral filling parameters. Most experts would agree that such a multiparametric approach mirrors the day-to-day operational assessment of diastolic function, wherein an expert attempts mentally to integrate multiple pieces of information by taking into account several variables, such as relaxation, pre-load, after-load, filling pattern, and even clinical setting. An e′ of 7 cm/s is never normal in a 40-year-old person, but it might be in a 70-year-old person, if the E/A ratio is 0.6 to 1.0, E/e′ is in the normal range, E velocity is 40 to 70 cm/s, and A velocity is 50 to 100 cm/s. Similarly, an E/A ratio of 0.6 is often considered normal for age in older patients, but this may be true only if E/e′ is at the lower end of the normal range. The prospect of accounting for these variables in a process of mental integration of the data is unappealing; clearly, there are limits to an informal approach to the assessment of diastolic function.

In contrast, for historical and/or practical reasons, virtually all attempts to formulate a quantitative operational assessment of diastolic dysfunction have focused only on univariable ranges in decision trees. Selmeryd et al. (3) successfully demonstrated the fallacies of using the multiple univariable reference ranges currently advocated in diastolic function guidelines. As illustrated by Selmeryd et al. (3), the complexity of the interacting determinants of cardiac diastolic function begs a broader view that

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includes a quantitative multivariable approach for acknowledging the real way a system functions. The problem of differentiating normal from abnormal could be circumvented if one were to conduct a single test on multiple dimensions rather than multiple tests on separate dimensions.

Selmeryd et al. (3) validated the clinical applicability of their approach by illustrating the prognostic value of the multivariable filling pattern models to determine outcomes in a 726-person community-based cohort and in 551 patients with myocardial infraction from the VaMIS (Västmanland Myocardial Infarction Study). However, their objective was simply to highlight the potential value of a multivariable reference range, and their work should generate further interest in the use of computational algorithms for refining classification schemes used for grading diastolic function. The current algorithm used only E, A and e′; other parameters such as right ventricular systolic pressures and left atrial volume were not incorporated into the model. The number of variables required to define diastolic dysfunction accurately remains an unresolved question, however, and needs to be dealt with in a similar fashion in future investigations.

From a data science perspective, diastolic function can be considered a "hidden" state that cannot be directly measured, but can be represented indirectly by the behavior of multiple clustered features (4). Because large numbers of measurements are made on the same "state," there is an inherent interconnectedness and a unique "structure" to these observations (5,6). One can take advantage of this structure to define a diastolic function grade; as the dimensionality of the problem increases, one could acquire an even better definition of the structure and more precision in analysis—a bonus. A high-dimensional state also causes a peculiar problem. There is a "curse of dimensionality" such that a statistically reliable result from a model requires exponential growth in the number of data needed to support the result with an increase in the number of dimensions (7,8). As a consequence, simple classification schemes perform poorly with the addition of new dimensions. Perhaps this effect may underlie the difficulties encountered with diastolic dysfunction algorithms that have attempted to involve several variables in decision trees, notwithstanding that clinical data supporting such algorithms have been sparse.

The paper by Selmeryd et al. (3) urges us to take a fresh look at existing echocardiographic standards and nomograms with new computational steps to develop multidimensional data integration as benchmarks for diastolic function assessments. Clearly, considerable research will be needed to generate appropriate features, to cull less relevant features of diastolic dysfunction, and to identify relationships among these features when constructing a high-dimensional structure of diastolic function. Moreover, using mathematical and statistical methods in the daily routine of the clinical laboratory remains an impossible task for clinicians. Therefore, unless such complex algorithms are automated and seamlessly embedded in routine workflow, they would remain beyond the realm of clinicians. Even more work lies ahead in overcoming culturally ingrained expectations of simpler algorithms while welcoming the nuances of complex computational algorithms. As new, promising, and readily available tools appear, they may tempt some clinicians to embark on a new journey to rethink how novel computational techniques can be used in practical laboratory work and for patient care.

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