Physiological Aging: Window of Opportunity*

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“It is much more important to know what sort of a patient has a disease than what sort of a disease a patient has.”
—William Osler (1)

Age-Associated Epidemic of Cardiovascular Disease (CVD)
As the world’s population lives longer, CVD evolves as the number one cause of disability and death (2). CVD currently accounts for approximately 45% of all deaths in persons age 85 years and older.

Limited Success
The incidence of CVD and 50% 5-year mortality rate of heart failure have remained unchanged for >2 decades (3). If the progression of CVD is not substantially prevented, the epidemic will expand and increasingly compromise the world’s health care resources and quality of life.

Physiological Versus Chronologic Age
Chronologic age and physiological age are rarely in sync. The “aging process” alters the substrate on which specific pathophysiological disease mechanisms become superimposed (4). There is a continuum of expression of cardiac structural and functional alterations that occurs with age in healthy humans, and these age-associated cardiovascular changes seem to have relevance to the steep increase in age-associated CVD (5). Chronologic age can define probable risk on the basis of expected programmatic change of natural markers (6). However, individuals will physiologically age differently within any peer group. The elapsed time since birth is not an effective measure of functional age. Attempts to manage a risk factor without defining and addressing the physiological substrate substantially contribute to the seemingly paradoxical outcomes in clinical trials (7). Prediction models, particularly those dependent on chronologic age, often do not adequately characterize disease severity.

In this issue of iJACC, Boyd et al. (8) aptly show that echo/Doppler features can be used to assess the physiological status into the eighth decade. Although the authors focus on left atrial size, they confirm that healthy living is best defined by a physiological profile as opposed to chronologic age. These observations increase our window of understanding regarding echo/Doppler as a multifeature biomarker capable of quantifying physiological age as a surrogate marker of an individual’s health status. Complex physiology is multivariable, and the use of a single biomarker will rarely characterize the physiological state (e.g., an enlarged left atrium can also be associated with completely normal diastolic physiology as seen in athletes and patients with chronic noncardiac disease) (9).

Defining Physiological Age
Until recently, determining physiological age has remained qualitative or based on individual or disparate seromarkers or biomarkers. However, CVD is complex and composed of multiple interconnected parts that, as a whole, exhibit 1 or more properties (behavior among the possible properties), which are not obvious from the properties of individual features, complex risk factors, or overt clinical disease (9). Multivariate physiologic models

*Editorials published in JACC: Cardiovascular Imaging reflect the views of the authors and do not necessarily represent the views of JACC: Cardiovascular Imaging or the American College of Cardiology.

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best provide quantifiable expression of physiological age relative to one’s chronologic peers (10).

**Prediction**

There is considerable misuse of the term *prediction*. The task today must transcend current reliance on diagnostic and prognostic prediction and evolve a new paradigm that focuses on physiological status and therapeutic value, where value implies prediction of improved clinical outcome at reduced cost (11). We must insist that virtually all risk models be shown to do what they are supposed to do—predict the prevention of clinical disease. The ability to predict or reclassify risk is beside the point. In the long run, a far superior approach to controlling complex cardiovascular disease will be prevention rather than treatment. The most logical approach is to use sets of highly associated data that replicate the physiological status of the patient (e.g., a quantifiable surrogate disease state) and then randomize treatment or control based on normalization of the surrogate profile. True surrogate status of a test only occurs when a change in the putative surrogate attributable to an intervention approximates a prediction of a change in the clinical end point. A model dependent on immutable chronologic age will not attain surrogate status. We must search for better ways of identifying at-risk individuals so aggressive preventive measures can be targeted while sparing those who are at no or extremely low risk and avoid the cost and side effects of unnecessary or potentially lifelong drug therapy. Multiple mutable echo/Doppler morphologic and physiological features (image biomarkers) have been amply validated and related to disease cause and effect (12–14). Cause-and-effect prediction models are as reliable as, and typically more reliable than, human experts (15). Although current risk models (e.g., Framingham Risk Score), biomarkers (e.g., C-reactive protein and B-natriuretic peptide), and advanced image technologies (e.g., coronary calcium score, carotid intima-media thickness) provide statistically significant risk prediction information, they add only modest incremental value and are not sufficiently precise to markedly improve clinical outcome (16). In addition, the premise of evidence-based medicine is to apply “average effects” to patients in prescribing treatments and preventive therapies (11). It is important to realize that tests that do not change disease management and substantially affect patient outcome are ultimately cost-ineffective. Valued prediction models ideally should be based on multiple quantitatively coded cues (i.e., elegant multivariable surrogate models) (17).

**Ideal Multivariable Biomarker**

An echo/Doppler model based on measured features fits the definition of an ideal multivariable biomarker, which approaches the status of a surrogate model. Interconnecting features must have close similarities to and most importantly obey the same fundamental rules as the emergent disease. Interrelated features more easily define the minimal requirements that best display disease behavior (intensity and response to treatment). Echo/Doppler goes beyond merely predicting risk. Echo/Doppler models can quantify the intensity of emergent CVD risk and more importantly assist prediction of clinical outcome (18).

The only economical means of containing an epidemic is prevention, which obligates prediction based on recognition, understanding, and quantification of the underlying cause-and-effect features, which are highly associated with an emergent condition. The echo/Doppler physiologic model meets most of the following ingredients: a collection of interacting features that are closely related and/or share various degrees of common information, interact with one another in a way that changes both and erases their dependence on initial conditions, measures features that adapt in accordance with changing performance, and helps define “open” systems that can be influenced by its environment or management.

Simple quantifiable features are easy to comprehend and comfortable in our minds. They remove ambiguities and reinforce a sense of understanding. An echo/Doppler surrogate model should be composed of a small number of simple interrelated numerical features that provide a method for anticipating complex events (predict), measure the magnitude of variance (quantify), and foster a more rapid and logical response to management of risk (prevention). Diseases are best defined as an interconnected network rather than a bag of independent unrelated chemicals (seromarkers), genes, or clustered risk factors.

**Window of Opportunity**

Despite the dazzling technical advances in cardiology, risk factor reduction and disease prevention in the aging population remain inadequate. There is an urgent need to look through the haze and find a reproducible means of elucidating the natural his-
tory, pathophysiology, and optimal diagnostic and management strategy for common medical syndromes. The benefits of estimating an individual's total physiological risk and treating accordingly are 2-fold. First is the direction of preventive efforts toward those most likely to benefit. Second is the reassurance and avoidance of side effects in low-risk persons who will derive less benefit, which also has economic implications. An opportune comprehensive multivariable echo/Doppler test is capable of rigorously defining pre-symptomatic CVD (10,12).

The transition from a subjective to objective definition of physiological aging is a major step forward. As Boyd et al. demonstrate (8), small aggregates of highly related numerical data can be transformed into quantitative surrogate models of CVD. Surrogate end points are intended to predict based on peer-reviewed evidence and used when it is difficult to collect suitable data based on clinical end points. Pre-emptive testing can provide information about a person's risk of a disorder developing and help with making decisions about medical management. The best high-risk approach to CVD evaluation and prevention lies in testing quantifiable physiological risk. Guidelines from the American Heart Association recommend CVD assessment beginning at 40 years of age and repeated every 5 years (or more frequently if risk factors change) (19). The most logical window of opportunity lies in the use of echo/Doppler imaging as a robust multivariable biomarker and the construction of elegant surrogate disease models.

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Key Words: aging ■ echo-biomarkers ■ physiologic aging ■ prediction.