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Precision Measurements to Assess Baseline Status and Efficacy of Healthy Living Medicine☆

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ABSTRACT

Precision medicine recently has gained popularity, calling for more individualized approaches to prevent and/or reduce chronic-disease risk and to reduce non-communicable diseases such as cardiovascular disease (CVD). Encompassed under Precision medicine initiatives is the concept of healthy living medicine (HLM), which emphasizes the promotion of lifestyle and behavioral practices including physical activity and healthy dietary pattern. Precision measurements have the potential to improve the understanding of how risk factors influence disease trajectory, and further inform on how to precisely tailor clinical strategies to manage risk factors to prevent disease manifestation, and refine therapies according the patient's demographic, environment, and disease etiology. The purpose of this review is to summarize the application of established and emerging measurements that may be used in HLM to manage and optimize care in CVD prevention.

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Healthy living (HL) medicine (HLM) is a concept that considers not only the support of HL principles[1] but the reversal of the principles that might be characteristic of an unhealthy lifestyle, which increases the risks of cardiovascular (CV) disease (CVD). HLM consists of four key components: 1) moving more and sitting less; 2) consuming a healthy diet at the appropriate caloric load; 3) maintaining a healthy body weight; and 4) not smoking.[2] Utility of HLM may be used to prevent CVD especially in populations with elevated risks. Precision medicine focuses on tailoring the approach to prevention and treatment by

Abbreviations: BMI, body mass index; CFR, Cardiorespiratory fitness; CPET, Cardiopulmonary exercise testing; CRP, C-reactive protein; CV, cardiovascular; CVD, cardiovascular disease; DXA, dual-energy x-ray absorptiometry; FMD, Flow mediated dilation; HL, health living; HLM, healthy living medicine; Il, interleukin; MET, metabolic equivalent of task; NO, nitric oxide; PA, physical activity; PWV, pulse wave velocity; VO_{2max}, maximal oxygen consumption; VO_{2peak}, Peak oxygen uptake.

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taking into account individual variability in the etiology and taxonomy of health outcomes, in addition to their environment, physical activity (PA) levels, and other key factors.[3] Thus, to obtain a deeper understanding of the mechanism of disease, refine disease risk assessment and prediction, and develop targeted therapies for various disease, warrants the need for more precise measurement tools (e.g., diagnostics, screening and prevention tools) with innovative applications in various aspects of health care.[3] It is also critical to have precision measurements that can be used to evaluate baseline status and risk classification that may quantify disease susceptibility in developing intervention and assess the progress of an individual throughout the course of the intervention. This review summarizes the measurements that may be utilized in order to achieve HLM in CVD prevention in the context of precision medicine.

CVD and outcome measures

CVD is a leading cause of death globally and has been an important public health issue.[4] It causes a negative economic impact due to medical expenses and loss of work productivity. The underlying cause of CVD is multifactorial, and predisposition is often dependent on the non-modifiable factors (e.g., age, sex, race/ethnicity) as well as modifiable lifestyle/behavioral factors (e.g., unhealthy diet, low PA, and tobacco use). The American College of Cardiology and American Heart Association recommend that adults aged 20 to 79 years should be screened for traditional CVD risks (i.e., age, sex, overweight and obesity, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, use of anti-hypertensive therapy, diabetes, and current smoking) and a 10-year risk of developing CVD should be calculated in those aged 40–79 years using the Pooled Cohort risk equation.[5] These traditional CVD risks usually present in response to unhealthy lifestyle/behavior, which highlights the importance of measuring these risk factors in HLM,[6] including intervention selection and goal setting. Routine assessment of these risk factors is instrumental for evaluating individual response to and adoption of a prescribed standard of care “intervention” and progress throughout the course of care.

While screening tools such as the traditional CVD risks can effectively identify individuals at high CVD risk, greater efforts improve the understanding of how risk factors manifest into overt CVD and how to tailor clinical methods to precisely manage CVD risk factors and refine therapies according to patient demographics, environment, and CVD etiology. This review will highlight the application of established and emerging precision measurement tools (Table 1) that may be used in HLM as markers of CV health to optimize care of practice.

Cardiorespiratory fitness

Cardiorespiratory fitness (CRF) has been recognized by the American Heart Association as a vital sign of health metric due to the added value of CRF in the prediction of various disease risks, particularly CVD.[7] Cardiopulmonary exercise testing (CPET) is commonly utilized to objectively evaluate exercise tolerance and functional capacity in healthy individuals and patients with various cardiac conditions, such as heart failure.[8] CPET offers the researcher or clinician a plethora of information such as test duration, electrical activity of the heart, subjective symptoms, and oxygen saturation that can be used for patient outcome measurements.[9] The information gained during the CPET can be documented for future use in the prescription of precision medicine and CVD risk classification. For example, heart rate reserve, or the difference between resting heart rate and maximum heart rate, represents an individual's appropriate CV response to exercise, and is used to inform and individualize exercise prescriptions to optimize CV health. Among all the measures derived from CPET,[7] maximal oxygen consumption (VO_{2max}) has been widely utilized and is considered as the gold standard for measuring CRF.[7]

VO_{2max}

VO_{2max} represents the ability of oxygen transport/utilization in the body and is defined as a plateau in VO_2 as workload increases.[7] It is largely determined by genetics but can be altered by aging, disease status, and physical activity. With a higher VO_{2max}, a person is generally able to perform aerobic activities to a greater extent and expend more

Table 1
Established and emerging precision measures in health living interventions.

Outcome	Technique	Measurement	Advantages	Disadvantages	Connection to CVD
Cardiorespiratory fitness	CPET	VO_{2max}	Established guidelines and references Used to prescribe an individualized exercise treatment	Need spirometry and gas analyzer Criteria of VO_{2max} may limits interpretation	A strong predictor of CVD and all-cause mortality
Body composition	DXA	Total body fat mass Fat free mass Bone mineral density Nonbone lean tissue	Standardized calibrations Short time period Tracking small changes in abdominal fat Sensitive to identify individual and ethnicity difference	Expensive Equipment cost although accessibility is better in clinical and research setting	A predictor of CVD and all-cause mortality Important to measure the risk of sarcopenia and osteoporosis to prevent functional decline and sedentary lifestyle
Vascular function	US imaging	FMD	Well validated Non-invasive Correlates with coronary metrics Established guidelines	High Operator skill required Need US machine No established references	Independent predictor associated with adverse CV outcomes. in some but not all studies; adds little to reclassification
	Tonometry	PWV	Well validated Reproducible Non-invasive Easy to perform Established guidelines and references Short time period	Composite measure of structure/function	An independent predictor of CVD
Inflammation and oxidative stress		hsCRP IL-6, IL-18 TNF-α	Commercially available kits Used to understand the mechanism	Clinical importance is not clear Cost, time and accuracy of measurement	CV risk and the measure may be used in clinical decision

CPET = Cardiopulmonary exercise testing; CV = Cardiovascular; CVD = cardiovascular disease; DXA = dual-energy x-ray absorptiometry; FMD = flow-mediated dilation; hsCRP=High-sensitive C-reactive protein; IL-6 = Interleukin-6; IL-18 = Interleukin-18; PWV = pulse wave velocity; TNF- α = Tumor necrosis factor- alpha; US = ultrasound; VO_{2max} = maximal oxygen consumption.

energy than an individual with a lower VO_{2max}. Alternatively peak VO_2 may be used in individuals who are physical inactive or at higher risk of CVD and unable to achieve their personal VO_{2max}. VO_{2max} is assessed during a maximal graded CPET (commonly on an uphill treadmill) either by a spirometry or can be estimated from heart rate at given submaximal workload. The choice of the test depends on subject ability, equipment availability, and other factors.[7]

Growing evidence has demonstrated the prognostic value of VO_{2max} in presumably healthy individuals as well as those with varying amounts of comorbid conditions.[7] For example, lower VO_{2max} has shown to be associated with traditional CVD risk factors[10] and future CVD events.[11] In terms of survival cost, a decrease of 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$ in VO_{2max} (equivalent to one metabolic equivalent of task [MET]), has been evidenced to increase risk of all-cause mortality ≈15% and CVD mortality ≈19%.[12] Reference values of VO_{2max} based on age and gender-specific reference have been established,[13] therefore allowing clinicians to develop appropriate exercise prescriptions that not only provide patients with an individualized and realistic goal in terms of CRF but also provides them perspective on how they can optimally change their CVD risk classification. Leveraging VO_{2max} in HLM is vital for promoting CVD prevention in high-risk individuals and developing and tailoring a strategic plan of action for managing and treating CVD.

Body composition

Obesity, defined as excessive body weight due to fat accumulation, affects >40% of US adults[14] with prevalence rates varying by age, gender, race/ethnicity, socioeconomic and/or education status.[15] Obesity is associated with increased risk of several non-communicable diseases including CVD, diabetes and various cancers,[16,17] and is thus, considered a high priority intervention target in HLM. Guidelines recommend annual screening for obesity using body mass index (BMI) to estimate body fat and indicate CVD risk.[16] However, antiquated measures such as BMI, a general measure of excess weight, or waist circumference, are often criticized given their limitations in distinguishing between fat and lean mass, and their inabilities to address obesity-related disease risk. Refinements in obesity measurements that are cost-effective, and allow for more precise and accurate assessments of health risks have been developed. Dual-energy x-ray absorptiometry (DXA), in particular, has emerged as a criterion method for assessing regional and whole-body soft tissue composition which may help to improve CVD risk classifications in various populations.[18,19]

Dual-energy X-ray absorptiometry

DXA applies dual x-ray beams with distinct energy levels to identify the elemental composition of soft tissue[20] and specifically quantifies the amount of whole-body and regional bone mineral density, total fat and nonbone lean tissue.[20] DXA measures of bone and soft-tissue are validated[21] and demonstrate high correlation with other criterion methods.[22] Likewise, the accessibility of DXA, combined with its ease of use and low patient burden (low-cost, low-radiation, non-invasive) make it more feasible to use in clinical and research settings compared to magnetic resonance imaging or computed tomography.[18] DXA has recently gained popularity for its ability to characterize fat patterning and quantify body fat distribution (e.g., subcutaneous and visceral adipose tissue), critical elements of HLM and CVD risk management.[23,24] Further, DXA's ability to more precisely assess small changes in abdominal fat during weight loss and maintenance therapies and with high sensitivity,[18] makes it superior over anthropometric measures (e.g., BMI, or waist and hip circumference measures) to track individual progress throughout the course of an intervention and refine approaches as needed. Importantly, assessments of lean mass and bone mineral density by DXA are used to identify patients at high risk of sarcopenia, osteoporosis, and frailty, morbid conditions that are common in elderly CVD patients,[25–28] particularly those with heart-failure,[29–31] and have been associated with worsening CVD outcomes and disease prognosis, and CVD mortality.[31] As emerging evidence suggests, measures obtained by DXA, though not traditionally viewed in the context of CVD risk, potentially may serve as prognostic indicators of CVD by identifying individuals who may likely benefit from preventative intervention and informing of tailored clinical approaches that may effectively manage CVD and multi-morbidity.

Emerging precision measurements in HLM & vascular function

Over the past two decades, vascular function including endothelial function and arterial stiffness has become an emerging target for the prevention and treatment of CVD. Aging, unhealthy lifestyle, or disease status cause structural and functional vascular changes, leading to endothelial dysfunction and arterial stiffening. Both endothelial dysfunction and arterial stiffening are involved in the development of atherosclerosis and are predictors of CVD.[32–35] Vascular function in health and disease has been extensively studied in laboratory and clinical research. The advance in imaging technology and applanation tonometry make the non-invasive measurement of vascular function feasible and accessible in a clinical setting, providing prognostic information to health care providers and potentially guiding patient care in HLM.

Flow mediated dilation (FMD)

Endothelium, the inner lining of all blood vessels, regulates vascular homeostasis by releasing various vasodilators and vasoconstrictors.[36,37] The most potent vasodilator produced by the endothelium is nitric oxide (NO), which diffuses into vascular smooth muscle cells and causes vasorelaxation. NO is known to have anti-inflammatory, anti-thrombotic, anti-coagulant, profibrinolytic, and anti-hypertrophic effects.[36] NO bioavailability is determined by endothelial function, and loss of NO bioavailability as a result of endothelial dysfunction may induce abnormal vasoreactivity. Impaired endothelium-dependent dilation is the signature feature of endothelial dysfunction. It can be assessed non-invasively by measuring brachial artery FMD, a change in vessel diameter in response to flow. Briefly, an ultrasound image of the brachial artery is taken by a high-resolution linear transducer at rest and during hyperemic activity (increased blood flow) by inflating a pressure cuff on the forearm to at least 50 mm Hg higher than systolic blood pressure for 5 min, and then deflating it rapidly. During hyperemic activity, the artery dilates due to NO release in response to shear stress and maximal dilation usually occurs within 2 min after cuff deflation. FMD is commonly expressed as maximal % change in diameter during hyperemia relative to the resting.

FMD specifically reflects the nature of conduit artery endothelial biology and atherosclerosis process such that this measurement tool is considered the standard tool of assessing peripheral conduit vascular function.[38] Individuals that have, or are at high risk of CVD commonly present with delayed or reduced vasodilation.[39] Epidemiological evidence suggests FMD serves as an independent predictor of CVD,[32,40] as a 1% increase in FMD has been associated with 13% reduction in risk of pooled CV events.[33] In contrast, some studies show FMD alone does not add additional information to traditional CVD prediction. The discordant findings may be due to the fact FMD is influenced by age, gender, or cardiovascular risk profile.[41–43] FMD may be improved via HLM such as PA/exercise,[44] healthy diets,[45] reductions in hypercholesterolemia,[46] and/or body weight loss.[47] When utilizing FMD as a CV outcome in HLM, it is important to consider both subject characteristics as well as assessment procedure.

At present, standardized protocols for data collection are carried out by highly trained operators and typically conducted in the morning, with subjects resting in supine for at least 20 min, fasting overnight, and abstaining from medications, alcohol, caffeine, tobacco or physical activity. Besides, other factors such as sleep duration also influences

FMD.[48] The recording of the subject's lifestyle metrics may help to elucidate individual variance in FMD and inform of HLM decision making. While high reproducibility in carrying out FMD is evident, feasibility and comparability in a clinical setting are notable limitations. However, newer technologies in FMD application, such as an adjustable clamp for transducer stabilization, a commercially available software for wall tracking and analyzing, and even a robot-assisted ultrasound system may resolve the issue and ensure data quality.[49] The cost of such technologies is relatively inexpensive especially with the existing access to echocardiography equipment or vascular ultrasound. Alternatively, portable ultrasound, which is a compact instrument that provides immediate results, may be more suitable in clinical settings to help facilitate a more streamlined approach to patient care.

Pulse wave velocity

Arterial properties determine vascular function and physiological responses. For example, elastic arteries such as aorta buffer sudden increases in pulsatile flow and energy and maintain microcirculation.[50] Arterial stiffening due to both structural (e.g., increased collagen) and functional (e.g., endothelial dysfunction) vascular changes leads to elevated blood pressure, increased wave reflection and wasted energy of the heart. This could also lead to end-organ damage including the kidney and brain.[51] The hemodynamic changes caused by arterial stiffening may further increase the risk of atherosclerosis as well as CVD.

The gold standard measure of arterial stiffness is pulse wave velocity (PWV), which measures how fast pulse waves travel in a specific arterial segment. PWV is assessed by taking the measurement of carotid to femoral PWV or aortic PWV and is calculated as the ratio of the distance to the time delay between the two recording sites. Measurement of PWV include several non-invasive methodologies such as ultrasound and magnetic resonance imaging.[51] Recently, a newly-developed cuff-based device with the use of a tonometer allows the simultaneous recording of pulse waves at the carotid and femoral artery and its validity and reliability have been established.[52,53] The cost of the device is modest, the measurement does not require a high degree of operator skill and can be taken within a short amount of time (<30 min). PWV should be measured in duplicate after at least 10-min resting in supine with an additional measure if the difference between measures is higher than 0.5 m/s.[51]

PWV has been extensively utilized in research as an independent predictor of CVD,[34,35,54] as 1 m/s increase in PWV has been associated with a 7% increase in risk of future CVD event.[34] PWV is suggested to improve CVD risk classification beyond the traditional standard of care.[34] Further, reference values of PWV, based on age, gender, and CVD risk profile, have been developed[55] with a cut-off point of 10 m/s indicating increased arterial stiffness and subclinical organ damage.[56] Consequently, PWV may be decreased by aerobic exercise,[57] healthy diets,[58] and/or weight loss[59] but the effect of these interventions may be influenced by individual characteristics and physiological difference including blood pressure and heart rate.[51] Although long-term intervention may be needed to induce adaptations in PWV, resistance exercise,[60] caffeine intake,[61] increased inflammation,[62] use of cigarette,[63] and other factors may increase PWV, even acutely. Recording sleep duration, diet including levels alcohol and caffeine consumption, physical activity, medication and tobacco use may also be helpful to interpret PWV in HLM. In individuals with central obesity, the measures of distance between carotid and femoral arteries over the body surface may be overestimated due to wider waist circumference, thus influencing PWV value.[64] Recently, a distance formula based on age, gender, body weight, height, blood pressure, and heart rate has been developed,[65] which eliminates measurement error and at the same time maintains the prognostic values of PWV. PWV may not only provide a strategy to identify and prevent CVD events, but may also be used for early detection of CVD-related damage, and should be included into routine clinical care and to serve as a CV outcome of HLM.

Biomarkers

The links of inflammation and oxidative stress in CVD have been extensively studied and several biomarkers have been identified. C-reactive protein (CRP) is one of the most promising inflammatory biomarkers that is associated with several CVD outcomes.[66] The American College of Cardiology/American Heart Association suggests high-sensitive CRP ≥ 2 mg/L may indicate an increase in CV risk and the measure may be used in clinical decision.[5] Some upstream biomarkers of CRP such as interleukin (IL)-6, IL-18, and TNF-α have also emerged as independent predictors of CVD.[67] Oxidative stress describes the imbalance between oxidant and anti-oxidant in favor of the former.[68] Several studies have shown that oxidized low-density lipoprotein-cholesterol may be associated with CVD outcomes.[69,70] Although the clinical importance of oxidative stress biomarker is not clear yet, from a pathophysiological view, food containing anti-oxidants may provide benefits in improving CV health. Therefore, measurements of oxidative stress have a potential role in guiding diet selection and evaluating intervention efficacy. Both inflammatory and oxidative stress biomarkers can be measured by commercially available kits. A challenge to applying these biomarkers in HLM is the measurement cost and time. Newly-developed technology now can analyze multiple biomarkers at a time with a small amount of blood sample. In addition, a computer-assisted device can decrease measurement error. Most importantly, future studies are still necessary to investigate how these biomarkers improve the current understanding of traditional CVD prediction.

Conclusion

Precision measurements have made a significant impact on the clinical and research aspects of patient care. The national research program from the National Institute of Health (All of us: https://www.researchallofus.org/) looks to promote individualized medicine by creating surveys in order to measure risk, identify biological markers, differences in response, and new classifications for disease among many other goals of the program. The concept of precision medicine would greatly benefit from the implementation of this program. Research would be able to look at common correlations and may influence the precision medicine and HLM. While this review mentions some of the factors that are considered during selection of outcome measurements to be utilized, there are an abundance of factors to consider when selecting outcome measurements. Contraindications, precautions, feasibility and other extraneous variables that may influence the results of the outcome measure should also be considered in choosing a precision measurement in HLM.

Conflict of interests/disclosures

None of the authors have any conflicts of interests with regard to this publication.

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