View Point

Need for a Noninvasive Diagnostic Platform for Early Detection and Management of Cardiometabolic Disorders

Gundu H. Rao, PhD, Pratiksha G. Gandhi, MD, *Minnesota, USA*; *Mumbai, India*

ABSTRACT

Background: There is a great need for the development of a noninvasive comprehensive diagnostic platform, for early detection of cardiometabolic disorders, such as hypertension, central abdominal obesity, metabolic syndrome, type 2 diabetes mellitus (T2DM), various vasculopathies, heart disease, and stroke. Several studies have demonstrated the usefulness of monitoring health of the blood vessels by using techniques that measure, intima–media thickness (IMT), pulse wave velocity (PWV), ankle–brachial index (ABI), carotid duplex ultrasound (CDU) index, vessel wall plaque volume (3D carotid ultrasound). Although so many methodologies are available for early detection of altered vascular function, the most widely used method is monitoring aortic pulse wave (PWV). With the advance in technologies, now it is possible to use multiple technologies and build a comprehensive risk assessment platform. It is also possible to add capabilities for risk prediction in such a platform. Availability of such a diagnostic platform will facilitate the surveillance of cardiometabolic disorders at the community level. To illustrate the usefulness of such a comprehensive approach for early diagnosis of metabolic diseases, in this article we have used "RISC" platform used by the Life Span (TOI sponsored) in India, as an example. However, we feel that there is great opportunity as well as challenge for further improvement of such applications. (J Clin Prev Cardiol. 2014;3(3):93-8)

Introduction

South Asians (Indians, Pakistanis, Bangladeshis, and Sri Lankans) have a very high incidence of cardiometabolic disorders, including hypertension, abdominal obesity, metabolic syndrome, T2DM, heart disease, and stroke (1–3). According to the World Diabetes Federation, currently there are more than 65 million diabetics in India and an equal number of prediabetics. This number is estimated to double in the next two decades. Once this disorder is diagnosed, there is no better alternative than to effectively manage the risk factors. Therefore, it is essential to develop early diagnostic methodologies for risk assessment, risk management, and prevention. In view of these observations and speculations, it is essential to develop a robust prevention strategy and appropriate action plans. With the increasing popularity of the interventional approaches, there is very little attention to preventive medicine approaches and holistic management of chronic diseases. In addition, there are no simple noninvasive methods available to detect early signs of vascular diseases. In this overview, we will present our views on challenges, opportunities, and future of preventive medicine in India.

Since we are discussing the early detection and monitoring of vascular dysfunction, historically, the only well-known method for monitoring vascular function has been the science of arterial pulse monitoring. From the ancient times to the present time, vascular pulse generated by the heart beat is considered very important for the diagnosis of the vascular function in health and disease. Pulse is often monitored in all systems of medicine, including Indian Medical System as a part of the clinical evaluation of patients' overall health (Sage Agastya's Treatise on Pulse Monitoring: Indus Valley Period 3500–1700 BCE). We should take advantage of this knowledge and draw from it every detail that is capable of giving insight to the physiology and function of the circulatory system. Measurement of the pulse by sphygmometer was described in the journal *The Lancet* as early as in 1834 (Volume 1, pp. 22–7). The title of the article described this instrument as the one which makes every action of the arteries apparent to the eye. In the same journal almost 40 years later, value of pulse, for diagnostic, prognostic, and therapeutic indications, were described (1875, Volume 106, pp. 441–3).

In modern times, Frederick Akbar Mohamed was the first to establish the use of pulse wave velocity (PWV)

From: Lillehei Heart Institute, University of Minnesota, USA (G.H.R.) IPC Heart Care, Mumbai, India (P.G.G.)

Corresponding Author: Gundu H Rao PhD
Lillehei Heart Institute, University of Minnesota, USA

Email: gundurao9@gmail.com

analysis for diagnosis of vascular dysfunction (4). He described the normal radial wave pressure waveform and the difference between radial pressure wave and the carotid wave. He also described the effect of high blood pressure on radial waveform and the effect of ageing on vascular physiology and function. PWV is measured by devices that use either probes or cuffs to noninvasively track the speed of blood flow in meters per second. One measurement is taken at the carotid artery and one at the femoral artery, and the difference between the two – calculated by the device – is the current gold standard measure of aortic stiffness. The slower the PWV the better indication that your arteries are nice and elastic and distensible. Results of a meta-analysis of clinical studies was published in the *Journal of American College of Cardiology* (5) and recommendations for PWV were included in the recent European Society of Hematology hypertension guidelines, noting that the technology is already being widely employed as a measure in hypertension and vascular-medicine clinics in tertiary centers across Europe and Australasia (*Eur Heart J*. 2013). This has been aided by the increasing availability of simple-to-use, noninvasive commercial devices to assess this parameter.

Anesthesiologists have been using this technology in the management of critical care patients for monitoring hypoxemia. All oximeters by and large are fundamentally photoelectric plethysmographs. By and large, PWV application has been basically ignored. PWV data from plethysmographic analysis indeed provides useful data on the cardiovascular conditions of the patients in critical care as well. Although, arterial pressure contour analysis for estimating human vascular properties was reported as early as in 1976, a simple, easy-to-use device was not available till the University of Minnesota researchers developed a CV-Profilor (1988) and offered a test called Cardio101, which took just 20 minutes for pulse wave analysis at a cost of US$101 (6–8). The CV-Profilor, a Solutions Engineering Project for Hypertension Diagnostics of Minneapolis, MN, USA, was featured on CBS news as an innovative approach to heart health. This device began as a University of Minnesota research (as were the now famous; heart and lung machine, pace maker, and bi-leaflet heart valves) and with Solutions Engineering expertise, resulted in a full turnkey product including software engineering, and analog and digital electronics. The device features the design and development of a patented sensor, touch screen, and embedded PC design. These devices collect 30 seconds of blood pressure waveform data from a small artery and a big one, and perform an analysis of the digitized blood pressure waveforms, and generate a CV-Profile report that contains information on the blood pressure, pulse pressure, body surface area, body mass index, both C1-large and C2-small artery elasticity indices. Changes in small artery elasticity have been shown to be highly predictive of cardiovascular disease (CVD). Promotional materials boasted that the device would identify heart disease at its earliest stage and that too in people with no symptoms. They hoped and anticipated its use in all major cardiac clinics. The US clinics have been slower to adopt this approach for monitoring vascular dysfunction.

Since I was quite interested in technologies that were capable of monitoring vascular function and dysfunction, I tried to get some clinical studies done on the CV-Profilor in India, especially in the healthy populations. However, the clinicians were more interested in using it as an additional diagnostic device for already sick patients, rather than do any field studies to evaluate whether the device can indeed detect heart disease patients with no symptoms. It was also the time when the studies on endothelial dysfunction was in the news and based on some of the findings related to this newly discovered vascular abnormality the industries developed Viagra, as a medication for correcting erectile dysfunction. Aaron Kelly and associates at the St. Paul Heart Clinic, Minnesota, used CV-Profilor to demonstrate the role of exercise in improving endothelial dysfunction in obese children (9). Since the CV-Profilor was quite expensive for the Indian market, we looked for an indigenous device capable of doing such pulse wave analysis. Since we were at the time promoting the CV-Profilor in India, I invited scientists from Genesis Medical System (GMS: www.genesisimedicals.com) of Hyderabad to Pune to see a demonstration of CV-Profilor. Staff of GMS invited me to Hyderabad and demonstrated their device. I was quite impressed to see the demonstration of their device called Periscope. At the time of this writing, the staff of GMS informed me that they also have a diagnostic platform called DiabLab for early detection of diabetes. This device is a combination of various POC devices on a single platform, which can be used to detect arterial stiffness and ankle-brachial index (Periscope), autonomic nervous system (ANS) functions (CanWin;

VarioWin), peripheral nervous system (ThesioWin), pulmonary system (SpiroWin), etc. However we have suggested to them to develop all-in-one single platform, which can be used as a comprehensive cardiometabolic risk profiler (CMRP). We are working with this group to develop the improved version of CMRP with risk profiling and risk prediction capabilities.

According to some sources, digital pulse analysis (DPA) is the next-generation use of PWV technology for monitoring PWV. It uses measurements of reflected infrared light from the blood. Similar to pulse oximeters, it uses a finger probe to monitor the blood flow velocity. DPA uses infrared light through the fingertip and obtain pulse wave information with the light absorbing characteristics of hemoglobin. A photo diode detects changes in the amount of light absorbed by hemoglobin, and its output measured in waveform is termed photoplethysmography (PTG). The Meridian DPA (Pulse Wave Technologies, Austin, TX, USA), according to the developers, provides information on arterial wall stiffness (also called PTG) and determines the biological age of the arteries. The device runs on an external computer and performs two separate scans: one for the arterial stiffness and another for the ANS (heart rate variability [HRV]). DPA's printouts include information on mean heart rate, missed heart beats (arrhythmias), level of arterial stiffness (seven types), waveform of PTG, eccentric construction (left ventricle ejection level), arterial elasticity, remaining blood volume, waveform of HRV, Balance of the ANS (SNS vs. PNS), stress reaction, mental stress, physical stress. Scores are expressed as color-coded (green orange and red) buttons or an actual number.

Everist Health of USA (Ann Arbor, MI, USA), which has developed a noninvasive sensor technology for a device called ANGIODEFENDER, claims that their device is capable of making early diagnosis of atherosclerosis and CVD years before a patient has detectable symptoms. According to the information provided on their website, AngioDefender system measures the health of the endothelium – the single-cell-thick interior lining of all the blood vessels, using a process called flow-mediated dilation (FMD). The device runs through a series of inflations and deflations using a cuff similar to blood pressure cuffs and analyzes the endothelium's response to increased blood flow. Then combining the data from blood pressure and pulse wave analysis derives, the %FMD scores are calculated. Dr Bhargava and associates at Medanta - The Medicity, New Delhi, used this device to monitor endothelium-dependent brachial artery flow mediated vasodilatation in patients with diabetes mellitus but without CVD (10). They found that the endothelial function as assessed by FMD was significantly impaired in diabetics compared to nondiabetics in the absence of CVD. In later studies, they also used Periscope to monitor arterial stiffness and demonstrated the importance of arterial stiffness as an important prognostic marker for cardiovascular events. According to their findings, in North-Indian subjects without known CV disease, arterial stiffness was significantly increased in hypertensives and was positively correlated with both systolic and diastolic blood pressure (11). They also showed all measures of arterial hypertension improved with control of blood pressure.

Using arterial tonometry (uses an array of pressure sensors pressed against an artery), Mitchell and associates evaluated central (carotid) and peripheral (carotid-brachial) PWV in the Framingham Heart Study offspring cohorts, who were free of clinical CVD. They found an age-related increase in aortic stiffness as compared with the peripheral artery stiffness (12). In a later study, this group used proportional hazards for CVD as well, for computing the risks and concluded that higher aortic stiffness as assessed by PWV is associated with increased risk for first cardiovascular event. Aortic PWV improves risk prediction when added to standard (Framingham) risk factor profile and, therefore, may represent a valuable biomarker for CVD risk assessment and prediction (13). There are several devices that can monitor PWV. Purpose of this effort is not to review all the work on this subject, but to take a critical look at how one can develop a comprehensive noninvasive diagnostic platform, for monitoring and management of cardiometabolic risks. If we can develop a cost-effective noninvasive point-of-care (POC) device, then we will be able to deploy these diagnostic platforms at the community level and provide risk assessment and risk prediction profiles for healthy populations as well as for those "at risk" of developing cardiometabolic disorders. With this idea in mind, we developed our first POC device, a noninvasive glucose monitor in India. Our patented device, like the photoplethysmograph, uses a photo diode and monitors blood glucose using near infrared spectrum.

To accomplish our goals, we need a multifunctional diagnostic platform. Therefore, we have approached Bio Medical Electronics Group of BMS Engineering College, as well as National Design Research Forum (NDRF), Bangalore, to help us develop such a medical device development platform. Genesis Medical Systems, Hyderabad, India, is working for several years on the development of noninvasive POC devices for cardiovascular applications. Since they already have several individual devices, they can make such a comprehensive CMRP to meet our requirements. We are collaborating with them not only in the development of CMRP, but also in the validation studies of their all-in-one device under development. In the mean time, we are looking at the available POC devices, which can be used for early detection of cardiometabolic disorders such as hypertension, glucose intolerance, T2DM, and its clinical complications. LD Technologies, Miami, FL, USA, specializes in the development of noninvasive POC devices. They have put together a platform called "RISC" (for Life Span, India), which uses ANS tests, HRV tests, sudomotor function tests, and The TM-Oxi system. The diagnostic platform used at the IPC Heart Care (TM-Oxi), Mumbai, India, and the Life Span Kiosks (RISC) in different cities in India is a combination of many devices and uses photoplethysmography, spectrophotometry, oscillometry, and galvanic skin response technologies and displays data rapidly. The scores for various functional tests are color-coded (green, orange, yellow, and red) and printed out graphically as well as digitally. It generates impressive diagnostic reports with some recommendations.

The ANS tests monitor the health of the nervous system in the healthy and diabetic population. Diabetics are at higher risk for developing diabetic autonomic neuropathy (DAN) and cardiovascular neuropathy (CAN). Sudomotor function is performed to detect skin blood flow (microcirculation) and C-fiber density for early detection of peripheral neuropathy. TM-Oxi system monitors functional oxygen saturation, pulse rate, and blood pressure. According to a brochure used by Life Span, the "RISC" tests comprehensively investigate 30 vital cardiometabolic health indicators. The tests include screening for insulin resistance and impaired glucose tolerance. It determines the optimum functioning of sympathetic and parasympathetic nervous system and checks for deterioration of muscle and nerve reflexes. Sudomotor test measures the extent of neural response and detects nerve damage (neuropathy). Cardiovascular health is also assessed by determination of ventricular function and hemodynamic analysis. Blood pressure and lipid markers are also assessed as indicators of chronic or symptomatic hypertension.

A general review on the use of these technologies for measurement of vascular function brings us to some major concerns. Can they accurately measure multiple health parameters? Why are these noninvasive devices not used in major hospitals and clinics? Why are these technologies still restricted for research purposes? Looks like it is the lack of robust clinical data to support the value of these noninvasive technologies which is the main factor in restricted use of these devices. There has been one meta-analysis of studies (12 studies with over 15,000 patients) on PWV, published in the *Journal of the American College of Cardiology* (5), which confirmed that it is predictive for total CV events and mortality (around a 20% increase in risk for one-SD higher PWV). A study by Mitchell and associates in which they were able to use the PWV data for improving the standard Framingham risk score also supports these findings. In spite of the fact that PWV analysis can be performed by a variety of devices, there is no comparative study to assess the merits of various devices available in a clinical setting and to test the superiority or inferiority of these tests against whatever so-called "gold standard tests" available. For instance, Salvi and associates compared three frequently used devices: the Complior and Pulse Pen, which determine aortic PWV as the delay between carotid and femoral wave, and the Pulse Trace, which determines the stiffness index by the most commonly used photoplethysmographic waves, acquired on the finger tip (14). These investigators found the reliability of the Complior and Pulse Pen devices in estimating PWV, whereas they concluded that the stiffness index determined by Pulse Trace was not a good surrogate for the PWV. These researchers appealed for an evaluation and comparison of the different devices to standardize the PWV measurements and establish reference values to be used for clinical and research settings (14). In view of these observations, we are developing a device testing and certification platform in India.

We are excited that we have a noninvasive diagnostic platform (TM-Oxi and RISC by LD Technologies), which can perform a variety of tests and provide information on 30 different cardiometabolic health

indicators. We are equally excited, that the prestigious Times of India Group has joined in this Herculean effort of educating the public about the need for early detection and management of risk for cardiometabolic disorders. They also have promoted the establishment of novel modern kiosks for the diagnosis of these risks at various cities. However, we feel strongly that there is a great need to validate the data generated by these kinds of devices so that the clinicians have total confidence of what they are finding and interpreting. One could use variety of methodologies to validate the data made available by such noninvasive devices. Perfecting the performance of such devices is crucial for their effective use in surveillance and prevention programs. In addition, as the researchers at the University of Minnesota have done, we can also build upon the strength of such diagnostic platform and develop not only risk assessment but risk prediction capabilities. Duprez and Cohn at the University of Minnesota use a variety of tests to grade the status of the cardiometabolic disease in their patients (15). They use seven vascular tests: large and small artery elasticity (CV-Profilor), resting blood pressure (BP), exercise BP response, optic fundus photograph, carotid intimal-thickness (IMT), and microalbuminuria. They also conduct three cardiac tests: electrocardiography, N-terminal pro-B-Type natriuretic peptide (NT-pro-BNP), and left ventricular ultrasonography. They have developed a global model that consists of composite disease markers called the Rasmussen Disease Score (15). Each of the 10 tests is scored 0 for normal, 1 for borderline risk, 2 for abnormal. The total score for any individual may range from 0 to 20. Based on their years of experience, Cohn and associates at the University of Minnesota feel that management of the disease itself is more important than the management of the risk factors.

We the members of the South Asian Society on Atherosclerosis and Thrombosis (www.sasat.og) also feel that this approach of managing the disease is better than just managing observed risks. Having said that, we also feel that there is a great need to develop a simple enough methodology to follow the progression of the disease. For instance, David Spence and associates at the Roberts Research Institute, Ontario, Canada, have shown that 3D ultrasound measurements of changes in carotid plaque volume (CPV) could be used for monitoring lipid-lowering therapies (16). What we need today is a combination of these POC methodologies for early detection of the altered physiology and function of blood vessels (16–20). In addition, develop the ability to add other observed risk factors to the data collected from such devices to improve the risk score so that one could use such comprehensive approach to the early detection of vascular dysfunction, follow the progression and regression of the vascular disease, and manage these diseases effectively. We are indeed trying to put together such a diagnostic platform (CMRP) in India.

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