INTRODUCTION

In a recent review in the New Engl J. Medicine titled, “NEJM Journal Watch Cardiology Top Stories of 2019, Krumholz,” the guest editor writes, “Finally, an important study reminded us that our evidence in cardiology, despite our progress, remains too thin. Investigators found that fewer than 10% of the American College of Cardiology/AHA guideline recommendations are supported by strong evidence. This is a call to action for more and better research in the future.”[1] These observations made by the investigators suggest that little progress is made in the evidence-based management of vascular dysfunctions. Furthermore, it seems like the management of cardiovascular diseases (CVDs), is more or less limited to the therapeutic interventions of modifiable risk factors for CVDs. Doctor Jay Cohn and Dr. Daniel Duprez of the University of Minnesota have argued in favor of an early identification of the vascular disease through simple screening tests. They have developed a ten point-test screening algorithm, which they have been using for quite some time for the management of cardiometabolic diseases.[2]

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Atherosclerotic CVD, especially coronary heart disease, is the number one cause of death worldwide. In our monograph on coronary artery disease, we refer to this condition as “vascular disease” rather than heart disease as ischemia due to poor blood circulation precedes the tissue injury to the heart. Detection of subclinical carotid, coronary or femoral vessel atherosclerosis, improves the risk prediction and management of the progression or regression of the disease. However, there is no simple non-invasive methodology to monitor the flow velocity of regional vascular beds, calculate fluid dynamics, and develops proprietary software and algorithms for risk assessment and management.

The relationship between vascular injury, inflammation, endothelial dysfunction, hardening of the arteries, subclinical atherosclerosis, and thrombosis is complex, especially in the post-stenotic flow field. Gandhi and Rao have described a non-invasive method, which uses spectral analysis of photoplethysmography (PPG) to evaluate the CV risk. The TM-Oxi system developed by the LD Technologies of Miami, Florida, uses a pulse oximeter and an automatic oscillometry blood pressure monitor managed by proprietary software. The PPG provides the measurements of relative blood volume in the fingertip during cardiac events. The first derivatives of PPG peaks are used for heart rate computing and the second derivatives for more accurate recognition of the inflection points of the original beats. In brief, the ratio of the amplitude of this waveform provides information on the relative degree of arterial stiffness. Over thousand patients have been screened at our IPC Clinic in Mumbai, India, using this technology. These studies have confirmed the presence of significant endothelial dysfunction in the diabetic population.

We would like to use thin film, flat panel piezo sensors, or modified pulse oximeters, using a flexible, organic, light-emitting diode display, and pin photodiode (thin film) sensor technology, to obtain pulse waveforms at various pulse pressure points, and calculate flow velocity measurements so that we can develop information about regional blood flow dynamics. The pulse oximeter combines the two technologies of spectrophotometry (which measures hemoglobin oxygen saturation) and optical plethysmography (which measures pulsatile changes in arterial blood volume at the sensor site). In the proposed studies, we will use the photo-plethysmography to compute the flow velocity of arterial blood at different regional beds. We also would like to explore other options such as the use of ultrasound imaging, thermal imaging, and to follow blood flow dynamics in peripheral arteries and veins. Studies have shown that biological imaging with carbon nanotube and dot fluorescence agents in the near-infrared (IR) region, can reduce the tissue scattering, reaching deeper penetration than the traditional imaging techniques.

Infrared thermography (IT) is a noninvasive, real-time diagnostic method that requires no contact with the patient and has broad spectrum of potential applications in neurosurgery. It has been previously demonstrated with high sensitivity and specificity to detect cerebral blood flow changes. IR thermal imaging of brain temperature variations is useful for evaluating cortical activity and disease states such as stroke. The temperature changes depend on a balance between changes in the heat generation from normal metabolic activity, and in the heat generated by the flow of blood. It has been shown that IR imaging of cerebral arteries performed using a sensitive, high-resolution camera during surgery, would permit changes in arterial blood flow to be visualized immediately, thus providing real-time assessment of brain perfusion in the involved vascular bed. As the heat emitted from the skin reflects the flow of blood, measurement of the heat emission gives a measure of blood flow. In a study done by researchers in London, UK, the overall diagnostic accuracy of thermography was 91% and the accuracy in diagnosing stenotic or occlusive disease in an internal carotid tree was 88%. Thermal imaging has been successfully utilized in the assessment of cerebral blood flow changes in normal and pathological brain tissue using an IR camera.

**DISCUSSION**

When we look at the blood vessel anatomy, average lumen diameter (D) and vessel wall thickness (T) vary considerably. According to published literature, the vessel anatomy is as follows: Elastic artery (D: 1.5 cm, T: 1.0 mm); muscular artery (D: 6.0 mm, T: 1.0 mm); arteriole (D: 37.0 um, T 6.0 um); capillary (D 9.0 um, T: 0.5 um); venule (D: 20.0 um, T: 1.0 um); and vein (D: 5.0 mm, T: 0.5 mm). Elastic or conducting arteries contain large amounts of elastin, which enables these vessels to withstand pressure fluctuations. Muscular or distributing arteries deliver blood to specific body organs have the greatest proportions of tunica media and are more active in vasoconstriction. Arterioles are the smallest vessels and allow for the exchange of nutrients between the blood and interstitial fluid. Shown in the Figure 1, is a human cerebral artery tree, displaying the main stem of the carotid artery and profuse arterial branches of small arteries. One can see the main carotid artery and varying sized vessels leading to the arterioles. Similar supply channels occur throughout the body to supply oxygen and nutrients for various organs and tissues.

In an earlier article, we have discussed the importance of flow velocity, fluid dynamics, vascular function, and dysfunction. Alterations in the vessel wall physiology and compliance of the vessels and the changes if any, in the blood flow velocity, are the earliest stages of vascular dysfunction that could be detected. There are several devices available in the market that can monitor changes in the flow velocity and provide information on endothelial dysfunction. Some of the devices in use include CV Profilor (Hypertension...
PWV increases with stiffness of the arteries. The PWV is a measurement used for evaluating arterial stiffness. After the blood rushes out during contraction, pressure pulses travel from the heart to the peripheral arteries. This causes a sound that can be heard with a stethoscope. According to the researchers who have developed the periscope (Genesis Medical System, Hyderabad, India: genesismedical.com), and TM-Oxi (LD Technologies, Florida: www.luteck.com). The majority of the people who suffer heart attacks have no symptoms, making prevention very difficult. However, now with the availability of these devices, we will be able to identify heart disease (vessel wall disease or dysfunction) at its earliest stage and in people with no symptoms. In spite of the advances made in the diagnostic medical device development, we still do not have a simple hand-held, point-of-care, monitor for diagnosis, and management of vascular dysfunction.

HD (www.hypertensiondiagnostics.com) of Minneapolis, Minnesota, has developed a method for non-invasively measuring the elasticity of large and small arteries, of which small artery elasticity is the earliest and most sensitive marker of CVD. One of the tests that the University of Minnesota uses in their ten-point risk assessment is CV Profilor. The device collects 30 s of blood pressure wave form data from a small artery and a big one, performs analysis of the digitized blood pressure waveforms and generates a report that contains information on the blood pressure, body surface area, body mass index, and both C-1 large and C-2 small artery elasticity indices. According to the researchers who have used this device, changes in the small artery elasticity have been highly predictive of CVD. Genesis Medical Systems of Hyderabad (www.genesismedical.com), India, have developed a simple non-invasive oscillometric device (periscope) to monitor pulse wave velocity (PWV) in small arteries. The report generated by this system, provides 8-s tracings of electrocardiography, all pressure pulse waveforms and calculated results. PWV is the speed at which the blood pressure pulses travel from the heart to the peripheral artery, after the blood rushes out during contraction. This measurement is used for evaluating arterial stiffness. PWV increases with stiffness of the arteries. The PWV is considered one of the most important clinical parameters for evaluating CV risk, and therapeutic efficacy. We are trying to explore this methodology to develop wearables capable of providing useful flow dynamics data on regional vascular beds.

Currently available methods to monitor the altered flow of blood include the carotid artery scanning by Doppler ultrasound or deep vein scanning for monitoring deep vein thrombosis. We are in the process of developing proprietary software and needed modification in the way scans are done to obtain 3D ultrasound measurements. In our attempts to search simple, cost-effective diagnostic tools, we are seriously considering IR imaging of the vessels of the eye, to obtain the health of the circulatory system. There are considerable improvements in the use of optical fundus cameras. Fundus photography is a valuable clinical tool for evaluating the progression of retinopathy in individuals and in participants in clinical trials. Fundus autofluorescence (FAF), for example, is used for monitoring macular degeneration and other various retinal disorders. FAF can be used for fluorescein angiography or optical coherence tomography and thus can be used to elucidate disease pathogenesis, diagnose, and monitor disease progression and evaluate novel therapies. The advantages of a fundus camera include color imaging capability. Forus Health, Bengaluru (www.forushealth.com), India, has developed the 3nethra classic, which is a compact, portable and easy to use non-mydriatic digital imaging device. It is designed to acquire, display, store, and transmit images of the posterior and anterior surfaces of the human eye. Early detection of diabetic-retinopathy saves diabetics from losing eyesight. Forus 3nethra system is a simple to use, portable, and cost-effective device for following diabetic retinopathy-related damages.

Shown in the Figure 2 are fundus photographs of a low risk individual and a moderate risk individual. Despite the equal duration of diabetes in both the individuals, early signs of diabetic retinopathy are visible in the fundus photographs of the moderate risk individual. In addition to microaneurysms, which induce such vascular dilation, small spot hemorrhages occur, which are described as “dot hemorrhages.” FAF imaging has been effectively used as a non-invasive tool for the detection of calcium emboli, as well as atherosclerotic plaques in the retinal artery. Near-IR imaging modality is being widely used for the detection of lipid content in coronary plaques. These two simple non-invasive techniques, FAF, and IR fundus imaging have been used for detecting asymptomatic or atypical emboli, even before vascular occlusion occurs.

We are very much interested in developing diagnostic devices that can follow the flow dynamics in the blood vessels of the eye using IR imaging systems. We are also interested in using confocal microscopy as well as optical coherence tomography, non-invasive imaging techniques, to follow the
morbidity of blood vessels of the eye as a means to study subclinical atherosclerosis and its progression.

**Thermal imaging for monitoring vascular dysfunction: A case report**

At Aarca Research Pvt. Ltd., Bengaluru, India, we use FLIR-E85 series thermal imaging camera to obtain thermal scans of body surfaces for monitoring thermal variations. In a routine thermal imaging process, we shoot the video at 30 frames per second for 1 min and capture 1800 frames of data. The data thus collected are computed and processed further, using proprietary software, to obtain patterns of thermal variation, and further graded for risk with 1–10, one being no risk and increases in the numbers indicating higher risk.

The diabetic, low-risk, and individual (A) are an 83-old male, residing in the USA for over half a century, with 10-year prediabetic condition, and 20 years of well-characterized diabetes, undergoing medical treatment which includes following medications; metformin (2 g), glipizide (10 mg), Januvia (100 mg), carvedilol (6.25 mg), lisinopril (20 mg), and atorvastatin (10 mg).

As shown in Figure 3, the mean interstitial glucose of this low-risk patient is 157 mg/dl, with a hemoglobin A1C (HbA1c) of 7.2%, suggesting well-controlled glucose metabolism. Risk score according to Aarca Research Product known as intelligent health risk assessment (IHRA) is for diabetes mellitus (DM) 1.2, hypertension (HTN) 2.9, and lipids (LP) 2.7 on a scale of 1–10. The moderate-risk individual studied (B) is also a male, 65-year-old with HTN (7 years), type-2 diabetes (25 years: HbA1c 6.5), hyperthyroid condition (5 years), and a smoker (12 years). Medications include Olsertain, Gucoril, Famcid, Thyrox, Moxavas, Ecospirin, Istamet, Trika, Remylein, Crevast, and Mirtaz. Risk score for this individual is as follows: DM 4.2, HTN 3.5, and LP: 3.1.

As it is visible in the images [Figure 4], the left hand is having an asymmetric temperature pattern for the moderate-risk individual [Figure 4b]. Furthermore, both hands are having colder fingers compared to the low-risk individual [Figure 4a] indicating signs of peripheral neuropathy.

As it is visible in the images [Figure 5], the left leg is having an asymmetric temperature pattern for the moderate-risk individual. Furthermore, both the legs are having colder regions of the foot [Figure 5b] compared to the low-risk subject [Figure 5a].

Despite being a long-term diabetic under tight glycemic control, the forehead and eye region has symmetric temperature pattern in the low-risk individual [Figure 6a]. As it is visible in the above images [Figure 6b], the forehead and eye region is having asymmetric temperature pattern in the moderate-risk individual.

Both the individuals studied are male with a diabetic condition for over 20-years and medical observation and robust modifiable risk management with appropriate medications. Despite the fact, that both are long-time diabetics and are under medical supervision, the older individual, over 82 years of age with a slightly elevated HbA1c, presents a better symmetrical thermal pattern in hands, feet, and face than the younger individual. This emerging technology also shows that even under the best of medical supervision, early signs of peripheral neuropathy can develop, as seen in the moderate-risk patient with HbA1c of 6.5. If using such non-invasive technology, early signs of vascular dysfunction can be diagnosed, one can initiate appropriate interventions to prevent further progress of the clinical complications.
Diabetes-mediated peripheral neuropathy is accompanied by the presence of symptoms or signs of peripheral nerve dysfunction in people with diabetes. Clinical diagnosis includes a test to determine loss of touch, vibration, and temperature sensitivity. Patients, who have lost 10-g monofilament sensation, are at considerable risk for developing foot ulceration. About 60–70% of all people with diabetes will eventually develop peripheral neuropathy, although not all suffer pain. Numbness is the most common symptom of nerve damage due to diabetes. People who lose sensation are the ones, most likely to get ulcers on their feet and end up needing amputations. Diabetic peripheral neuropathy has been defined by the Toronto Consensus Panel on Diabetic Neuropathy, as a “symmetrical, length-dependent, sensorimotor polyneuropathy, attributable to metabolic, and microvessel alterations, as a result of chronic hyperglycemia exposure and CV risk covariates.” Since the loss of sensation is a subtle change that occurs over a long period, there is a great need for the development of novel noninvasive methodologies, to follow microvascular dysfunction. We feel strongly that further improvements in thermal imaging with improved analytics and algorithms can indeed determine the early signs and microvascular diseases as well as peripheral neuropathy.

The Framingham heart study (FHS) is a project of the National Heart, Lung, and Blood Institute, USA, and the Boston University School of Medicine (www.framinghamheartstudy.org). Started in 1948, the family-based study developed much of the earliest scientific evidence of the relationship between CVD, smoking, obesity, diabetes, high blood pressure, and high cholesterol. Based on the collective knowledge gained by these studies, researchers formulated Framingham risk functions, risk score algorithms, and risk calculators. If one makes a search for information on CVD risk score, Google and other search engines provide links to a variety of sites, including risk score charts, European society of cardiology risk score, American heart association risk score for heart and stroke, the Reynolds risk score, Canadian acute coronary syndrome risk score, heart disease risk calculator (Mayo Clinic), ACC/AHA ASCVD risk calculator, and ASCVD risk estimator. Most calculators use a 10-year time frame (77%), but a few uses 5-year time frame (7%), 30-year (3%), and lifetime (7%) risk. Unlike this scoring system, we would like to develop vascular risk scoring, by computing the degree of block or hardening of the regional arteries, using flow dynamics data and proprietary software analytics and algorithms.

The FHS risk score and various modifications of such risk scored are more or less restricted to the prediction of CVD development or acute vascular events such as heart attack and stroke. We feel that there is a great need to develop, a robust risk score algorithm for vascular dysfunction. To accomplish this, we need to develop capabilities to monitor the flow dynamics of regional vascular beds. We have discussed the devices that have been used for the detection of hardening of the arteries (CV Profilor, Periscope, LD-Technologies). However, none of them have been validated for their specificity in determining endothelial dysfunction in population-based screenings.[10,19,30-32] We at Aarca Research Pvt. Ltd. at Bengaluru, are developing diagnostic devices for noninvasive monitoring of altered vascular flow in regional vascular beds, using wearable pressure sensors, for monitoring pulse waveforms, at various pulse pressure points. Such devices as well as improvements in ultrasound and IR imaging technologies will improve early diagnosis of both microvascular and macrovascular dysfunction.

By and large, in the majority of clinics, the progress of diabetes is managed by monitoring fasting glucose, postprandial glucose, or HbA1c levels. Despite robust management of the diabetes in the moderate-risk individual, we see early signs of arterial dysfunction, as evidenced by the thermal asymmetry and higher risk scores, compared to the low-risk individual. In view of this fact, the moderate-risk individual should be referred to the appropriate specialists, for further therapeutic interventions, to restore the blood flow to the affected areas. The cutaneous circulation, plays a pivotal role in the dissipation of heat during exercise, which is generated as the most abundant by-product of metabolism.[33] Kelly and associates from Minnesota demonstrated, that in the
overweight children and adolescents, C-reactive protein, a marker for inflammation was independently associated with fasting insulin. Just eight weeks of aerobic exercise improved fitness, HDL cholesterol, and endothelial function in this group.\textsuperscript{[34]} Naturopaths have been recommending message therapy to increase circulation of blood and for managing vascular dysfunction. We are trying to validate transdermal delivery of vasodilators or substrates for vasodilators, for restoring the blood flow in peripheral arteries. Korean researchers have demonstrated, the benefits of microcurrent stimulation on the foot blood circulation.\textsuperscript{[35]} Hyperbaric oxygen therapy has been shown to contribute to the healing of ischemic ulcerations in diabetic patients, and to improve several other pathological conditions.\textsuperscript{[36]} Several electric compression treatments are available for improving peripheral blood circulation. The patient should be tested again post therapy, with thermal imaging to monitor the progression or regression of the vascular dysfunction.

**CONCLUSIONS**

Diseases of blood vessels cause more morbidity and mortality than the combined impact of any other major non-communicable disease including cancer. We strongly feel that the development of a therapy system based on the management of disease of the vessel than management of the risk factors will yield better results and provide better opportunities for individualized therapy. Many methods are available, for risk profiling for the development of CVDs, as well as for predicating acute vascular events associated with vascular dysfunction. However, there are relatively few non-invasive technologies available for monitoring vascular dysfunction of various regional vascular beds. We have described in this article, a new and emerging technology, for monitoring blood flow or the loss of it, at regional surfaces by monitoring varying temperature patterns, using thermal mapping with proprietary software and analytics.

IT is a noninvasive, real-time diagnostic method that requires no contact with the patient and has broad spectrum of potential applications in neurosurgery. It has been demonstrated, with high sensitivity and specificity to detect cerebral blood flow changes. IR thermal imaging of brain temperature variations is useful for evaluating cortical activity and disease states such as stroke. The temperature changes depend on a balance between changes in the heat generation from normal metabolic activity and in the heat generated by the flow of blood. It has been shown that IR imaging of cerebral arteries performed using a sensitive, high-resolution camera during surgery, would permit changes in arterial blood flow to be visualized immediately, thus providing real-time assessment of brain perfusion in the involved vascular bed. As the heat emitted from the skin reflects the flow of blood, measurement of the heat emission gives a measure of blood flow at regional vascular beds.

In this article, we have briefly described an emerging technology of thermal imaging, to monitor temperature variations in the affected parts such as hands, feet, and face to show that this technology, can indeed diagnose the difference in the temperature variations between the skin surface of a low-risk individual, from that of an individual with moderate risk. This study also demonstrates that a robust control of hyperglycemia reduces, or prevents, the development of diabetes-related clinical complications. Need for the hour is the development of simple, cost-effective, diagnostic tools for monitoring early vascular dysfunctions of regional vascular beds.

**REFERENCES**

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