Emerging Technologies for the Management of Cardio-Vascular Health

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When we refer emerging technologies, we mean, -the state-of-the-art technologies, that are developing at the time of this writing. However, for someone who has completed half a century of research related to heart and vascular health, cutting edge technologies are ever evolving and to a great extent, responsible for the tremendous improvements made in cardiovascular research in the last few decades. In view of the rapidity in which the novel technologies are innovated and implemented, it is hard for scientists, clinicians, and researchers, to catch up with emerging technologies. Furthermore, there is a great disconnect between the innovator, product developer, research scientists, clinicians and the end users. When I started working at the University of Minnesota Medical School in 1970, Earl Bakken (Founder of Medtronic Inc, Minneapolis, MN) and Professor Walton Lillehei (Founder of St. Jude's Medical Inc, MN), had already developed a novel, fully implantable pacemaker. Fifty years of improvement in the original device resulted in the development of Medtronic heart pacing device, not much larger than a silver dollar, with the battery that lives close to a decade. Today's pacemakers weigh little more than an ounce and can be checked remotely via phone every few months, to verify a patient's heart rate and rhythm and evaluate the device's function and remaining battery life. Furthermore, all pacemaker vendors now have FDA-cleared MRI compatible pacemakers.

During early days, there was extensive collaboration between the Academia and Industry in such developmental work. If one does an internet search, for the top ten biomedical innovations, one can see prominently a list of innovations that the Cleveland Clinic has posted, which include: hybrid closed-loop insulin delivery system, neuromodulation to treat obstructive sleep apnea, gene therapy for inherited retinal diseases, unprecedented reduction in LDL-cholesterol, the emergence of telemedicine, next generation vaccine platforms, arsenal of targeted breast cancer therapies, enhanced recovery after surgery, centralized monitoring of hospital patients, and scalp cooling for reducing chemotherapy-induced hair loss. The area of medical innovation that is conspicuously missing in this list is the phenomenal developments in the area of cardio-valvular and cardiovascular research and their applications [1]. The field of cardiovascular medicine is rapidly evolving in pace with the advances in technology and engineering. For instance, cardiac pacing, has seen a series of game-changing innovations,

-low-power electronics, high density batteries, improved catheter delivery systems, and innovative software design.

On the other hand, a search on 'Emerging Medical Technologies', will reveal the ten leading technologies listed for 2020: 1) Dual-acting Osteoporosis Drug (romosozumab), 2). Expanded use of minimally invasive mitral valve (MitraClip) surgery, 3) Inaugural medication of transthyretin amyloid cardiomyopathy, 4) Therapy of peanut allergies, 5) Closed-loop spinal cord stimulation, 6) Biologics in orthopedic repair, 7) Antibiotic envelope for cardiac implantable devices for infection prevention, 8) Bempedoic acid for cholesterol lowering in statin intolerant patients, 9) PARP inhibitors for maintenance therapy in ovarian cancer, 10) Drugs for heart failure (forxiga) with preserved ejection fraction. A further search on the same lines, will provide an additional list of innovations, related to trends in cardiovascular technologies: Artificial intelligence and machine learning in cardiology, -includes automated ejection fraction (EF) calculations for point-of-care ultrasound systems. At the low end, AI algorithms are used to automatically detect arrhythmias and send alerts to patients, using wearables or smart phone-based apps, that record ECG. Examples of this technology include, Apple watch and the Kardia Alivecor devices [2]. Transcatheter mitral (TMVR) and Tricuspid valve (TTVR) interventions. In 2019, the FDA cleared the use of transcatheter aortic valve replacement (TAVR) for all patient surgical categories.

Wearable technologies aid patient monitoring, and currently, many individuals use wearable devices, to track their health using Apple Watch or Fitbit devices. Fitbit is sold in 110 countries and 28 million people use it to track their activity. Individuals who are 18 years and older, who use wearables, can join the Scripps Translation Science Institute (STSI), study and consent to share their activity data, by downloading the MydataHelps mobile app (www.detectstudy.org). STSI is now partnering with Fitbit, to enable users to synch their mHealth wearables with the national 'All of Us' research program. Virtual (VR) reality and augmented reality (AR), are now being used in several large cardiology facilities to train their staff. Abbott uses virtual reality simulator, to train interventional cardiologists, how to use its intravascular optical tomography (OCT) imaging technologies, to probe lesions in the coronary arteries, -to create 3-D renderings

of the disease vessel segments. Big data and structured reporting can help for mining big data for population health determinations, where risk factors for all patient records in health system can be automatically combed through, to identify patients at risk for certain diseases. Holographic procedural navigation in the Cath lab can be projected now, without the need for special glasses or visors. Robots in the Cath lab are a reality, with the availability of the Corindus CorPath system and the French-based Robocath. Virtual, Image-based fractional flow reserve (FFR) technologies are pressure wire-based flow measurements. Such technologies allow the user to virtually stent a vessel segment to determine the FFR value, if the vessel was opened to its native lumen size.

In the early days of cardiac research, device development and applications went hand in hand in terms of clinical diagnostics and therapeutics. Werner Forssmann, Andre F Cournand and Dickinson W Richards were awarded the Nobel Prize for their seminal work on cardiac catheterization, which revolutionized vascular intervention procedures [3,4]. Percutaneous coronary angioplasty was introduced by Gruentzig in 1977(5). It took a decade of evolution for further development and the use of first coronary stent. Since the earlier versions of the bare metal stents were associated with intra-stent stenosis, in 2002, drug eluting stents (DES) were introduced with anti-inflammatory or antiproliferative drug coatings [5, 6]. Applications of endovascular procedures have been expanded throughout the human body, for both occlusive and aneurysmal disease; arteries at the aortoiliac as well as for femoropopliteal levels [7]. At the time of this writing, interventional procedures are the preferred treatment option for peripheral artery disease. Furthermore, there are novel approaches available for expanding catheter-based interventions for all areas of the body. In the cardiac/vascular laboratories, new expansion areas will be in peripheral artery disease, critical limb ischemia, transcatheter valve repair and replacement technologies for all four heart valve positions. In a recent report, researchers from the University of Minnesota demonstrated, (using 3D printed patient-specific aortic root models with internal sensors) -that the use of internal sensor arrays in such models, can facilitate the optimization of bioprosthetic valve selections and in vitro placements, via mapping of the pressures applied on the critical regions of the aortic anatomies. The authors conclude, "that these models may pave exciting avenues for mitigating the risks of postoperative complications and facilitating the development of next generation medical devices [8].

Some of the other advances include, the use of more accurate electro-anatomical mapping systems and improved ablation catheter technologies, that will reduce intra-operative variability and improve success rates to 80-90% in the coming years. Electrophysiological implant devices will become much smaller and wireless, thus eliminating need for surgical pockets and venous leads for pacemakers. They will also have the capability to follow 24-7 monitoring, conducted via the web through remote monitoring. Artificial intelligence and machine learning technologies will be used, to track patient data and identify patients, who need follow-up, device reprogramming, and other interventions. We will also envisage development of novel approaches, for the use of simple wearable patient monitors, that will monitor activity due to lifestyle changes, new drugs. In addition, we will see the integration of technologies (IOT) and development of health portals, that can collect, collate and develop information of intending risks and alert the patients. There will be greater use of 3-D advanced visualization in cardiac imaging. In our earlier articles, we have articulated the use of 3-D imaging for carotid artery scanning, developed at the Robert Research

Institute, London, Ontario, Canada. David Spence and associates from Canada, have demonstrated that 3D plaque measurements can show large effects of statin therapy on atherosclerotic plaques, as well as provide useful information on vulnerable plaques [9].

Atherosclerotic plaque volume, composition, and morphology plays a critical role in the stability of the plaque and its vulnerability. For instance, statin use has been shown to reduce the plaque volume by lowering the lipid content of a plaque, or in other words demonstrates plaque regression [10]. However, recent studies have shown, that statin use increases coronary artery calcium (CAC) score significantly [11]. Increase in CAC has been shown, to contribute significantly to poor cardiac outcomes. On the other hand, researchers have tried to explain this phenomenon, -as a reflection of the effectiveness of statins, in lowering the lipid levels in atherosclerotic plaque. When the plaque volume reduces due to loss of lipids, the calcium score calculated per volume, seems to show increase in calcium, -and this 'observed increase in calcium' may not indicate, actual increase in coronary calcification. Fibrin plays a critical role in the stability of a clot. Despite this awareness, information on fibrin viscoelasticity, mechanical strength, and mechanisms of fibrin rupture remain unknown. A recent bilateral study, between the US and Russian scientists demonstrated, that rupture resistance of clots and thrombi, determines the incidence of thrombotic embolism, in pathological conditions associated with changes in cellular and molecular blood composition, such as hypo or hyperfibrinogenemia, variations in platelet or leucocyte count as well as hematocrit [12].

In our monograph on coronary artery disease, we described coronary heart disease (ischemic heart disease) as the disease of the blood vessels. Disease of blood vessel causes more morbidity and mortality, than combined impact of any other major noncommunicable disease. Vascular diseases are the number one killer and were the cause of 18 million deaths worldwide in 2017. We strongly feel that development of a therapy system, based on the diagnosis and management of the vessel wall disease, is superior to that based on management of modifiable risk factors. Having said that, we would like to inform the readers, that earliest signs of vascular disease is, when one can detect the alterations in the flow dynamics and resulting vascular dysfunction (also known as endothelial dysfunction). Currently available diagnostic technology is limited to various ultrasound monitoring modalities, that are used in the clinics to monitor alterations in carotid artery flow or the venous flow for the detection of deep vein thrombosis. There is a great need to develop noninvasive technology for monitoring subclinical atherosclerosis, venous clots, presence of micro thrombi, and in general alteration in the flow dynamics at various regional vascular beds [13]. In a short guest editorial, it is hard to cover all the novel and emerging technologies in cardiac and vascular research, readers are urged to refer to original articles and comprehensive monographs on this subject [13-21].

To create awareness, develop educational and preventive strategies, we started a professional society, -South Asian Society on Atherosclerosis and Thrombosis (www.sasat.org) at the University of Minnesota in 1993. As a part of this ongoing effort, we organized 15 international conference in India between 1994-2010. We also published four books on Coronary Artery Disease [22-25]. Despite these efforts, we feel that there is a disconnect between the emerging technologies, innovators, clinicians and researchers. From time to time, we make attempts to fill this void by writing editorials, mini reviews, and publishing monographs on selected areas of our research interest. As a part of our continuing effort to educate the scientific community, we also

review recent publications and summarize relevant information. Recently Professor UDI Nussinovitch (Applicative Cardiovascular Research Center (ACRC) and Department of Cardiology, Meir Medical Center, affiliated to Tel Aviv University, Israel) has published two books on Emerging Technologies for Heart Diseases (Elsevier). The Volume one covers the treatments for heart failure and valvular diseases. The book provides a comprehensive review of the latest therapeutic developments for heart failure, valvular disorders, myocardial ischemia and arrhythmias, and their clinical implications [26]. The Volume 2, in this series is about, -treatments for Myocardial Ischemia and Arrhythmias. This volume also covers comprehensive reviews on the latest therapeutic developments of heart failure, valvular disorders, myocardial ischemia, arrhythmias, and their clinical implications [27]. In addition to the usual therapeutic treatments, there are special chapters on, gene and cell-based therapies for the treatment of ventricular arrhythmias, supraventricular tachyarrhythmias, bradyarrhythmias; molecular and cell therapies for ventricular arrhythmias; gene and protein therapy approaches for cardiac neovascularization and novel treatments for hypertension.

For those readers who would rather read a simple version of the same complex topic, I suggest, - 'Invoking Your Inner Therapist in Heart Failure', written by Dr. Kris Vijay (Krishnaswamy Vijayaraghavan, Professor of Medicine, University of Arizona, Scottsdale Cardiovascular Center, Arizona.(kvijatmd@gmail.com), published by Spotlight Publishing, Good Year, Arizona. (<https://spotlightpublishing.pro>). This is a book about details of prevention to end stage of heart failure written in a lay community jargon with patient experiences, their stories and what the author has learned from them over several decades of clinical practice [28].

Heart disease is the leading global cause of death. According to the World Health Organization, number one cause of death globally, taking an estimated 17.9 million lives each year. Four out of five acute vascular events, are due to heart attacks and strokes. These deaths are preventable. In addition to the emerging technologies that we have briefly discussed in this editorial, there are thousands of health-related apps available for download. Since our interest is early detection of risk factors for cardiometabolic disease, management of risk factors, we have envisioned the use of emerging technologies at three phases of prevention protocol. The first phase is dedicated to population-based studies. Activity trackers can be used effectively, to develop a robust risk assessment and risk management strategies [2]. At the second level we advocate the use of dedicated devices such as ambulatory blood pressure monitors and continuous glucose monitors to empower patients [15]. The third phase deals with the robust patient care that can be developed using emerging technologies at the clinics, hospitals, and multispecialty healthcare centers. Medical innovations have contributed significantly, to the improvements in diagnosis and management of Cardiac and Heart health. We anticipate, that emerging technologies will play a greater role in early diagnosis of the risks, management of the risks, and providing better healthcare. The vision I have of the future technology applications is an information and technology information platform, that will be able to collect, compute, assess disease specific risks, create appropriate patient alerts, and suggest optimal interventions.

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