Artificial intelligence (AI), defined as intelligence exhibited by machines, conjures up images of HAL, the rogue computer in Stanley Kubrick’s epic 1968 science fiction movie, “2001: A Space Odyssey.” The idea of “intelligence” being incorporated into inanimate objects has been floated since antiquity. The first rudimentary AI programs were developed in 1951 to play checkers and chess. Since then, AI has expanded to almost every facet of modern life, including the medical field. The collaborative Mayo Clinic Cardiovascular AI team recently published the results of their study utilizing AI ECG analysis to predict the presence of left ventricular dysfunction in asymptomatic patients (Zachi I. Attia et al: Screening for cardiac contractile dysfunction using an artificial intelligence-enabled electrocardiogram. Nature Medicine 25:70-74, 7 Jan 2019).

Some Basics
Some common examples of machines that utilize versions of AI are the iRobot Roomba, which vacuums the floor and can navigate around obstacles; the Mars rovers Spirit and Opportunity; and Siri, Apple’s virtual assistant. These and most other devices utilize weak, or narrow, AI. They operate within a restricted range of pre-defined functions to accomplish narrowly demarcated tasks.

Deep learning – strong AI – is one of a family of machine learning methods based on learning data set representations. Advances in computing power so that large amounts of data can be quickly analyzed have made the application of AI to huge, complex data sets feasible. Deep learning architectures have been applied to diverse fields such as speech recognition, social network filtering, bioinformatics, drug design, and medical image interpretation.

Deep neural systems are comprised of a series of “layers”: an input layer, a cascade of processing units or hidden layers, and an output layer. Each of the layers is comprised of individual neurons which extract and transfer data in a hierarchical fashion into more composite representations. Data from one layer is processed and fed into the next layer. The basic scheme of a recurrent neural network is illustrated in Figure 1. Different types of neural networks have been developed; the type
of neural network employed depends on the type and complexity of analysis being performed. Because recurrent neural networks are not particularly good at image analysis, convolutional neural networks (CNNs) are commonly used for this function and are especially helpful in the evaluation of high-resolution medical imaging (Figure 2). Subtle variations in a data set can be identified, extracted, and compiled.

**CNNs have two functional components:**
- **Feature Extraction (Convolutional Layers)**
  Data from the input layer is fed into the hidden layers, which perform a series of convolutions, which are mathematical functions, and pooling operations which make assumptions about the data to downsize the number of parameters to analyze and neutralize the effect of changes in scale or orientation; computational cost is also reduced (Figure 3). Characteristic features in the image are detected during this process. For example, in a picture of a pig, this extraction process identifies four short legs with even-toed ungulate hooves, a curly tail, fat body, two pointy ears, and a snout.

- **Image Classification (Fully Connected Layers)**
  Here, the fully connected layers, in which each neuron in one layer is connected to every neuron in the adjacent layers, will classify the image based upon these extracted features. This process assigns a probability that the object in the image is actually what the algorithm predicts it is – that is, a pig. Well-designed classification layers avoid considering broad areas of possibilities that are unlikely to be relevant. A pig lives on land; therefore, ocean dwellers need not be considered.

**The Study**
Paul A. Friedman, MD, electrophysiologist and Chair of the Department of Cardiovascular Medicine at Mayo Clinic in Rochester, MN, spearheaded the study utilizing CNNs to analyze ECGs to predict the presence of asymptomatic left ventricular dysfunction (ALVD). ALVD is present in 3-6% of the general population, affecting more than seven million Americans. Risk increases with age; in the elderly, ALVD is present in 9% of individuals. Effective therapies exist and, if administered early, can reduce hospitalizations and mortality significantly. Yet, no ALVD screening tool exists that is inexpensive, widely available and noninvasive to facilitate broad and early intervention by general clinicians. Currently, the gold-standard screen for ALVD is echocardiogram, not readily available in non-specialty clinics. B-type natriuretic peptide (BNP) levels have been studied for screening purposes, but results have been disappointing, and the test requires invasive phlebotomy.

Dr. Friedman and his team envisioned screening for ALVD by subjecting the common and inexpensive electrocardiogram (ECG) to a custom-designed and trained CNN. Explains Dr. Friedman: “We hypothesized that the metabolic
and structural derangements associated with the cardiomyopathic process would result in ECG changes that we could reliably detect with a properly trained neural network.” ECGs and echocardiographic images from Mayo Clinic’s large digital database were used. From training inputs, the CNN generalized attributes to make predictions about images the network had never previously seen. Using Mayo Clinic stored digital data, researchers screened 625,326 paired ECG and transthoracic echocardiograms to identify the population to be studied for analysis. Because ECGs involve repeating complexes, both spatial and temporal dimensions were analyzed. They then trained and validated the CNN with patient data from 44,959 ECG-echocardiogram pairs. The network goal was to use ejection fractions (EF) ≤ 35% to identify low EF patients and refer them for more detailed follow-up exams.

The Mayo team tested the network on 52,870 patients reserved for external validation. Of those, approximately 8% had an EF < 35%. The sensitivity, specificity, and accuracy of the CNN were 85%, 86%, and 86%, respectively. “The network ranked 0.93 in its ability to flag low EFs – out of a perfect score of 1.0. To put this in perspective, a mammogram is 0.85. These results show the network is very robust,” Dr. Friedman says.

Additionally, when the network suggested a low EF based on ECG findings but the echo EF was normal, patients had an estimated five-fold increased risk of developing a low EF in the future. “This suggests that the network may reveal silent subclinical, metabolic or structural abnormalities hidden in the ECG,” Dr. Friedman says. Within the next year, providers at Mayo Clinic will launch a pilot study of the use of AI to detect ALVD in the clinical practice.

Within Mayo Clinic’s Cardiovascular Medicine Department, interdisciplinary teams are applying artificial intelligence to some of the most challenging clinical problems. Exciting examples include:
• Early risk prediction of conditions such as embolic stroke
• Heart monitoring and arrhythmia detection in smart clothing projects based on a textile computing platform
• Occult disease detection, such as identifying atrial fibrillation’s earliest, subclinical stages, through heart physiology signals transmitted by mobile electrocardiogram (ECG)

For more information about AI cardiovascular research at Mayo Clinic, please contact Dr. Francisco Lopez-Jimenez at (507) 284-8087.

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**IN THE NEWS**

**Children’s Hospital Colorado**

Children’s Hospital Colorado has joined the Mayo Clinic Todd and Karen Wanek Family Program for Hypoplastic Left Heart Syndrome (HLHS), along with Children’s Hospital of Philadelphia, Children’s Minnesota, and Children’s Hospital of Los Angeles in a nationwide HLHS consortium. The consortium was developed to give patients more options when it comes to participating in groundbreaking clinical trials and other research, no matter their location. “We are thrilled that Children’s Hospital Colorado has joined the hypoplastic left heart syndrome consortium because it brings the research to more patients who may have otherwise had to travel in order to participate,” says Timothy Nelson, MD, PhD, director of the Todd and Karen Wanek Family Program for Hypoplastic Left Heart Syndrome. “Individuals with HLHS now have more options at their fingertips, and the expansion of consortium members accelerates finding new and better solutions for these patients.” The team is addressing the various aspects of these heart defects through research and clinical strategies ranging from basic science to diagnostic imaging to regenerative therapies.

**IN THE NEWS**

Vishal Khullar, MBBS, has joined the staff in the Division of Cardiovascular Surgery at Mayo Clinic in Rochester, MN. He completed his residency training in cardiovascular and thoracic surgery from Bombay Hospital and Medical Research Center, Mumbai, India. He continued his training in advanced cardiovascular surgery at Mayo Clinic in Rochester, MN, and sub-specialization training in advanced aortic surgery, heart/lung transplantation and mechanical circulatory support at the Cleveland Clinic in Cleveland, OH. Dr. Khullar has unique skills and interest in heart/lung transplantation, mechanical circulatory support, and complex re-operative cardiac surgery.
Broadening the Perspective for Regeneration in the Heart

Stem cells, with their unique potential to transdifferentiate into different tissues, have transformed the way we think about how the body repairs itself. The first use of cytotherapy dates back to the 1950s when cells were utilized to treat hematologic malignancies. With initial successes, the paradigm of biologics-based therapies was expanded to include a spectrum of chronic diseases, culminating in the most recent example utilizing T-cells engineered with chimeric receptors (CAR-T) to treat refractory cancer. The cardiac regeneration effort at Mayo Clinic began 20 years ago. This work has since culminated in clinical efforts spanning beyond adult cardiology to also include cardiac surgery, pediatrics and vascular medicine, with active efforts in heart failure, Ebstein’s Anomaly, Hypoplastic Left Heart Syndrome, and refractory angina.

Cell Therapy in Practice

The discovery that stem cells derived from patients with heart failure had variable regenerative potency was a critical landmark. By identifying uniquely activated cues in regenerative sub-populations, cells from patients could be coaxed to adopt a highly regenerative state. Termed cardiopoietic stem cells, this specialized cellular population demonstrated a heightened aptitude towards cardiac repair. To standardize the assessment of therapeutic potency in the heart, a cardiopoietic index was developed to allow objective assessment of the regenerative potential of patient-derived stem cells. Moreover, clinical-grade production of these cells at scale provided the capability to translate this platform from the bench to the bedside. Following optimization of manufacturing algorithms for cardiopoietic stem cells, clinical trials (C-CURE and CHART-1) were executed in Europe using this platform developed at Mayo Clinic to test its safety and to obtain signals of efficacy. Indeed, this effort led the largest published clinical trial to date using cells in patients with chronic heart failure of ischemic origin. These clinical experiences provided unique insight into patient populations who would most benefit from cell-based therapy and offered a blueprint for how stem cells should be delivered.

Dosing and Delivery

Traditional small-molecule drugs have well-defined mechanisms of actions and processes of absorption, distribution, metabolism and excretion. The pharmacodynamics and pharmacokinetics that stand behind these actions are well understood. Case in point, oncologists have identified dose-response curves for the treatment of individual malignancies, as well as dose ceilings beyond which toxicity can be expected. In contrast, biologics-based therapies display intricate and still poorly-understood pharmacodynamics and pharmacokinetics, hampering proper dosing. As such, optimal cell dose and delivery frequency can be further refined. The large cohort of patients treated in CHART-1 allowed post-hoc subgroup analysis to demonstrate a bell-shaped relationship between dose and effect. Results showed that when a minimum threshold dose was exceeded, fewer injections provided improved outcomes. The trial also revealed that despite robust measures to ensure cellular uniformity, interpatient variability remains the biggest hurdle to achieving uniform improvement following application.

Next Generation Biologics

The cardiopoietic stem cell experience, along with other efforts within the Center for Regenerative Medicine by investigators in the Department of Cardiovascular Medicine, Cardiovascular Surgery, Pediatrics, Medicine, Transplant, Radiology, Laboratory Medicine, and more broadly across the Mayo Clinic enterprise, has created a team with unique expertise in product development, manufacturing, quality assurance and FDA-regulated clinical trial execution. To this end, the new challenge in this field is to take an inherently variable autologous (from the patient) cell population and engineer new platforms that provide reliability in dosing, potency and efficacy. With the emergence of automated bioreactor systems in manufacturing, synthetic messenger RNA platforms and increasing expertise in creating allogeneic (from the donor) master cell banks provide the opportunity to engineer allogeneic cell platforms devoid of the variability seen with their autologous counterparts. Beyond cell therapy, with increasing understanding of the mechanistic basis for regen-
Regenerative technologies devoid of cells would have the capability of activating repair-signaling pathways to mimic stem cell action in the heart. Since it is increasingly apparent that stem cell benefit is likely due to a paracrine mechanism of action, rather than direct integration, acellular approaches are of increasing interest. Implementation of a cell-free regenerative paradigm provides additional benefits including the ability to have clear dosing algorithms, assured homogeneity in function, and elimination of logistical hurdles that often complicate cell-based therapeutic models. The evolution of biologics-based technologies, in tandem with the 21st Century Cures Act, has encouraged a more rapid advancement of regenerative platforms.

Mayo Clinic has built new readiness in this space with dedicated infrastructure to serve as a supply chain for regenerative technologies and address unmet patient need. The Mayo Clinic regenerative portfolio builds on the already robust cellular effort to now implement trials using extracellular vesicles and gene therapy, a next chapter in the evolving regenerative toolkit.
Sudden cardiac death (SCD), the swift, unanticipated loss of life due to undetected coronary abnormalities and anomalies, remains an Achilles heel of contemporary medical practice. Within the field of cardiovascular medicine insights have emerged in identifying conditions that may be associated with SCD, allowing for either early intervention or prophylactic measures.

Congenital anomalies of the coronary arteries are purported to be relatively uncommon, but they contribute to the top three causes of SCD in those younger than 35 years of age. These abnormalities are clinically heterogeneous and may be simplified to those anomalies of origin, course or termination (Figure). Within these broad groups are predefined subgroups that have characteristics considered to be associated with SCD. To date, these anomalies are generally discovered incidentally, either in asymptomatic individuals who undergo testing for unrelated conditions or in symptomatic individuals in whom a broad net of testing is undertaken. When anomalies of the coronary arteries are discovered unexpectedly, it must be determined whether they require intervention and, if so, what type of intervention is required.

Unfortunately, the extent to which the various coronary anomalies portend SCD is still debated, and further conflict exists regarding the appropriate strategy of care. These issues are further complicated by the fact that research in the field is limited to small retrospective observational studies that limit the understanding of these anomalies. Despite these hindrances, the general community of cardiologists agree on a number of anomalies that require attention. The next intuitive step is to build centers of expertise that can serve as pillars of care, education and inquiry.

The Mayo Clinic Adult Congenital Heart Disease Clinic was originally established to serve those with congenital heart disease during an era when understanding of these complex lesions was evolving. Since its establishment, the clinic has grown to serve a wide number of individual patients from all over the globe. With the same mission statement to care for the sick and advance the science, a specialized sub-clinic devoted to the care and understanding of anomalies of the coronary arteries – The Coronary Anomaly Clinic – is now established with integration of clinical cardiologists, cardiac imaging specialists and cardiovascular surgeons with a focused interest in the field.

**Figure.** 3D volume-rendered images from computed tomography angiography demonstrating a congenital coronary anomaly with the left anterior descending artery (LAD) arising from the main pulmonary artery (PA).
New Treatment Options for ATTR Amyloidosis

Amyloidosis is a disease of protein misfolding leading to amyloid fibril deposition in organs and tissues throughout the body. Although previously considered to be rare, amyloidosis is increasingly recognized as an important cause of disease, especially heart failure. The misfolded protein aggregates into insoluble oligomers, which are cytotoxic, and rigid amyloid fibrils, which when deposited in tissue distort the architecture and cause organ dysfunction including the heart. Intramyocardial deposition of amyloid fibrils leads to increased wall thickness and ventricular dysfunction. Although there are over 30 different precursor proteins implicated that may form amyloid, only two commonly affect the heart: immunoglobulin light chain amyloidosis (AL) due to a plasma cell dyscrasia, and transthyretin amyloidosis (ATTR) due to misfolding of transthyretin (pre-albumin) which transports thyroxine and retinol binding protein.

Outcome of patients with cardiac amyloidosis depends on amyloid type and severity of cardiac dysfunction. Untreated patients with AL cardiac amyloidosis have a median survival of less than one year after the onset of heart failure. Although patients with ATTR cardiac amyloidosis have a more slowly progressive disease, the median survival after diagnosis is 3.5-4 years. Medical therapy for ATTR cardiac amyloidosis has only recently been proven effective, and treatment options are now rapidly evolving.

There are two types of ATTR: ATTRv, the hereditary form caused by pathogenic mutations of the transthyretin gene, and ATTRwt, previously known as senile systemic amyloidosis, in which a pathogenic mutation is not present. The inheritance pattern in ATTRv is autosomal-dominant with variable penetrance. Although most forms of ATTRv are rare, approximately 4% of the black population in the US carries the Val142Ile variant (legacy nomenclature VAL122Ile). Patients with ATTRv amyloidosis may present with a predominant neuropathic or cardiac phenotype or with an overlap of manifestations. Those with ATTRwt have mostly cardiac manifestations, with the exception of spinal stenosis, ruptured biceps tendon, and carpal tunnel syndrome, or with an overlapping phenotype. ATTRwt typically presents after the age of 60 and is more common in males, with symptoms of right heart failure, arrhythmias, and conduction system disease. Carpal tunnel syndrome is present in 30-40% of patients at diagnosis and usually precedes cardiac manifestations by 6-10 years, offering an opportunity for early diagnosis and treatment.

Treatment options for ATTR amyloidosis are rapidly expanding. Diflunisal is a transthyretin stabilizer that has been shown to slow progression of neuropathy in patients with ATTRv amyloidosis. However, the non-steroidal anti-inflammatory effects of diflunisal limit the ability to use this medication in patients with moderate or advanced heart failure. The observation that apolipoprotein in the transthyretin gene stabilizes the transthyretin protein in the setting of a destabilizing pathologic variant led to the development of a new drug, tafamidis, a benzoxazole derivative without non-steroidal anti-inflammatory properties. The drug binds to the thyroxine-binding sites and inhibits the dissociation of tetramers into monomers. Prior studies have demonstrated that tafamidis slows the progression of peripheral amyloid polyneuropathy in patients with ATTRv amyloidosis. This observation led to the design and implementation of the Transthyretin Amyloidosis Cardiomyopathy Clinical Trial (ATTR-ACT), a phase 3, multicenter parallel-design, double-blind, placebo-controlled, randomized clinical trial comparing tafamidis 80 mg and tafamidis 20 mg against placebo in patients with heart failure due to ATTR amyloidosis, NYHA class I-III.

Results of the trial, recently published in the New England Journal of Medicine (Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. NEJM 379:1007-1016; 13 Sep 2018), are very encouraging. In the analysis of primary endpoints, all-cause mortality (29.5% vs. 42.9%) and the incidence of cardiovascular hospitalizations (0.48/year vs. 0.70/year) were lower in those patients who received tafamidis than those who did not. Additionally, patients who received tafamidis had a slower decline in performance on both the 6-minute walk and KCCQ-OS score, with statistically significant benefit seen after six months.

Martha Grogan, MD, Director of the Cardiac Amyloidosis Clinic at Mayo Clinic in Rochester, Minnesota and study author, points out that the trial also raised intriguing questions. “Patients with less severe heart failure at the beginning of the trial had more benefit from treatment, suggesting that early diagnosis and treatment may be key to influencing the course of the disease,” she says. Additionally, reductions in all-cause mortality were not seen until 18 months and reductions in cardiovascular hospitalizations were not seen until 9 months after initiation of treatment respectively. “This delay in benefit may be due to the treatment time needed to affect disease progression,” says Dr. Grogan. Additional studies evaluating the efficacy of blocking production of transthyretin are in progress.
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