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CARDIAC NUCLEAR IMAGING (A CUOCOLO AND M PETRETTA, SECTION EDITORS)

Artificial Intelligence in Nuclear Cardiology: Adding Value to Prognostication

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Abstract

Purpose of the Review Radionuclide myocardial perfusion imaging (MPI) continues to be an accurate and reproducible method of diagnosing obstructive coronary artery disease (CAD) with predictive, prognostic, and economic value. We review the evolutionary potential of machine learning (ML), a subset of artificial intelligence, as an adjunct to MPI.

Recent Findings Applying the broad scope of ML, including the integration of deep learning, can leverage the knowledge representation and automated reasoning to detect and extrapolate patterns from high-dimensional features of MPI. There is growing evidence to suggest superior abilities of ML over parametric statistical models for predicting the presence of obstructive CAD, the need for revascularization, and the occurrence of major adverse cardiac events including cardiac death.

Summary ML is uniquely positioned to provide the next great advancement in the field of nuclear cardiology for improving patient-specific risk stratification.

Keywords Coronary artery disease · Myocardial perfusion imaging · Machine learning · Artificial intelligence · Nuclear cardiology

Introduction

Machine learning (ML), a subset of artificial intelligence (AI), is now pushing various fields of cardiology to transcend boundaries limited by conventional statistical approaches. The ripples of ML in cardiology are clearly being seen in the field of nuclear cardiology. Non-invasive imaging modalities are paramount in cardiovascular care by encompassing a clear role in diagnosis, outcome prediction, and patient welfare [1]. The sheer quantity of imaging data with each scan is rapidly rising with all diagnostic options which will exceed the capabilities of current software and imaging analysis [2]. As of now, nuclear cardiology is home to the largest number of fully automated approaches in comparison to other modalities [1, 2].

Coronary artery disease (CAD) is the leading cause of heart disease, is responsible for one in every five deaths, and is commonly encountered throughout the world [3]. As a direct ramification of this morbidity and mortality, there has been a gradual rise in the use of imaging approaches to predict the presence of underlying CAD [1]. The foremost difficulty in diagnosis and prognosis arises from related comorbidities and heterogeneous clinical presentations, which can alter the results in key diagnostic tests in nuclear cardiology [4]. This is possibly accredited to the utter magnitude of functional and perfusion variables at play. ML can extrapolate hidden patterns encountered in these modalities and can overcome existing difficulties to facilitate data-driven discoveries in nuclear cardiology (Fig. 1a). In this review article, we discuss the role of ML in paving the future of nuclear cardiology and how it adds value to prognostication in patient management.

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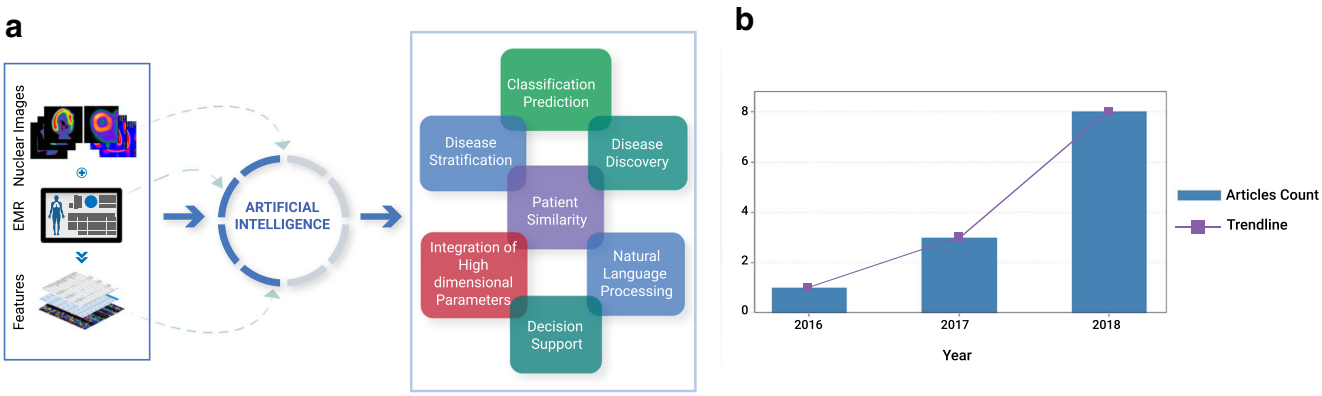

Fig. 1 **a** Flowchart showing the process of Artificial Intelligence (AI) in Nuclear Cardiology. The images from different modalities and electronic medical records including genomics can be combined to extract various features. They can either compositely be fed in to the AI and machine learning models or individually to extract meaningful interpretations in nuclear cardiology. **b** The growth of machine learning techniques in nuclear cardiology. The data was retrieved from PubMed between 2016 and 2018 using R package RISmed. The count of the publications of machine learning methods in nuclear cardiology went up noticeably in 2018 and is greater than the publications in previous 2 years combined showing the growing interest in machine learning in nuclear cardiology

Nuclear Cardiology

For several years, myocardial perfusion imaging (MPI) has served as a pillar of nuclear cardiology and as a cornerstone test in diagnosing obstructive coronary artery disease [5]. Approximately, 7 million patients undergo MPI per year [6]. As technologic advances evolve in radionuclide imaging, the spectrum of MPI continues to expand. For example, the transition from planar to tomographic imaging improved the predictive value of MPI. Once gated left ventricular ejection fraction was possible, this further provided prognostic knowledge in patient care with enhanced specificity. ML is positioned to provide yet another leap in the diagnostic accuracy of radionuclide MPI.

Diagnostic and Prognostic Capabilities of MPI

MPI has value in patients with intermediate to high probability of CAD, with well-defined diagnostic, prognostic, and economic advantages [5]. Given these inherent advantages, MPI has become a mainstay of non-invasive cardiac imaging for risk stratification of CAD [7]. Moreover, the diagnostic relevance of MPI may be overshadowed by its prognostic significance. There are two basic tenets of MPI: (1) a normal MPI has an excellent negative predictive and prognostic value with a very low incidence of subsequent cardiac events [5], and (2) the positive value of predicting cardiac events in patients with myocardial ischemia/jeopardized myocardium [1]. As myocardial ischemia increases, the risk of cardiac events increases proportionately. MPI can determine which patients require referral for coronary angiography and those who will benefit from coronary revascularization [1]. As a result, analysis of MPI studies can yield possible values of ischemia which dictate lines of management.

Developing accurate values from imaging data enables prognostication, therapeutic progress, and precise diagnosis. The necessity for quantitative analysis has propelled the growth of post-processing software. This facilitates the production of fully automated images from raw images virtually. Nevertheless, the physician must check the workflow and concur with the interpretations and closing report.

Importance of Quantitative Analysis

SPECT and positron emission tomography (PET) MPI play a critical role in CAD diagnosis by providing both ventricular function and myocardial perfusion information. Many of the fully automated processes exist predominantly in SPECT MPI while is it comparatively lesser with PET. Although full implementation of automated processing will occur in the near future, many nuclear cardiology laboratories continue to visually process the images. Quantification of the uptake of radioisotopes into viable myocytes is assessed using a 17-segment model of the left ventricular myocardium for calculating the intensity of uptake as well as the summed stress, rest, and difference scores [2]. These automated post-processing advances are superior to the visual approach which succumbs to interobserver [8] and intraobserver variability—irrespective of physician experience [9].

Accordingly, the automatic quantification of the myocardial perfusion is frequently used in cardiovascular care [10]. The perfusion imaging data from the computer is obtained and oriented to proper coordinates to generate a polar map. Pixels from test patients are compared with normal test scans stored in computer software. This comparative analysis

enables physicians to identify areas of reduced perfusion located in the polar map [2]. Active advancements in this process are an ongoing research.

Scope of ML in Nuclear Cardiology

The role of ML in nuclear cardiology is broad and its potential is limitless. ML can have capabilities of combing patient information in conjunction with imaging data to produce individual patient–oriented treatment plans or deliver precision medicine. For ML to replicate results close to human counterparts, it must learn in a unique way. ML works through a series of attempts to study the data and unravel hidden patterns [4]. The capabilities of ML augment proportionally as the data set becomes larger. Unfortunately, as the data set becomes larger, the interpretability of features can be lost [4]. ML consists of supervised, unsupervised, and reinforcement methods. In nuclear cardiology, supervised ML is frequently used (Fig. 1b). Supervised learning uses a dataset with classes or outcomes classified [11]. Unsupervised learning works with datasets with labels or annotations and uncovers hidden relationships present within the set of information [11]. Reinforcement learning utilizes certain reward criteria akin to human psychology [11]. Within unsupervised learning, deep learning is gaining significant traction in the field of cardiology [11]. It uses multiple layers of cells similar to neural networks present within the human brain. This particular sub-discipline is thriving due to significant leaps and bounds in computing capabilities and cloud infrastructures.

ML seeks to learn from the data without any supervision while conventional statistical techniques require labels to find relationship between variables [4]. The realms of both ML and conventional statistics have significant overlap and their roles need to be understood for researchers [4, 11]. In many ways, ML is dynamic, and it resembles the real world while conventional approaches are static. However, prediction is not a clear strength of statistics [4]. In contrast, ML algorithms can generate data driven predictions from data sets and have been quite effective.

ML Prediction of Coronary Artery Disease

Arsajani et al. conducted a study designed to improve the accuracy of MPI for CAD prediction by using a supervised learning algorithm in 957 studies by utilizing perfusion and functional variables [12]. Three hundred thirty-four patients had low likelihood of CAD while 623 correlated with invasive angiography [12]. The results were compared with automatic quantification software and 2 experienced readers. The sensitivity and specificity of ML was considered superior ($p < .005$ for all). The receiver operating curve (ROC) area under the curve for support vector algorithm (0.92) was statistically significant compared to both readers (0.87 and 0.88, $p < 0.03$).

Similarly, Arsajani et al. led another study to predict CAD by integrating clinical data and imaging features with ML algorithms to improve SPECT accuracy in 1181 patients [13]. A supervised ML algorithm or logit-boost was used in this study. The total perfusion deficit was calculated by automated quantification software and there 2 expert readers. The ML had similar accuracy to expert 1 but was better than total perfusion deficit supine/prone and expert 2 ($p < .001$). The ROC curve for the ML algorithm (0.94 ± 0.01) was superior to the total perfusion deficit and two readers with an extremely statistically significant difference. ($p < .001$). Arsajani et al. finally concluded that ML integration with clinical information was able to improve the diagnostic accuracy of MPI SPECT to match those of expert readers.

ML Prediction of Revascularization

Arsajani et al. investigated to determine if early revascularization in patients with suspected CAD by utilizing a ML approach by integrating clinical and imaging data in MPI SPECT patients for 713 patients [14]. Similarly, the study uses a logit-boost supervised learning algorithm. The prediction of revascularization by the ML algorithm was compared with two experienced readers by using imaging, quantitative, and clinical data. The sensitivity of the ML algorithm was similar to one reader. However, the specificity of the ML algorithm was found to be superior to both expert readers ($p < .05$) and similar to total perfusion deficit ($p < .05$). Interestingly, the ROC for the ML architecture was (0.81 ± 0.02) was similar to reader 1 (0.81 ± 0.02) but better than reader 2 (0.72 ± 0.02, $p < 0.01$) and standalone measure of perfusion (0.77 ± 0.02, $p < 0.01$). The study clearly demonstrated that the ML approach was comparable to expert readers and better than MPI SPECT alone for predicting revascularization in patients.

ML Prediction of Cardiac Death

Alonso et al. created a ML algorithm to approximate the risk of cardiac death derived from an integration of adenosine myocardial perfusion SPECT with clinical information [15•]. Subsequently, this was compared with logistic regression. A supervised ML algorithm was used in the study. These models were exposed to 122 probable clinical predictors in a total of 8321 patients and 551 cases of cardiac death [15•]. The ROC

curve was used to measure accuracy for all groups. Interestingly, the logistic regression was outclassed by the ML architecture (AUC = 0.76; 14 features). The ML algorithm clearly showed superior accuracy (AUC = 0.83; $p < .0001$; 49 features). However, the least absolute shrinkage and selection operator (LASSO) model required the least number of features (AUC = 0.77; $p = .045$; 6 features). They concluded that LASSO performed much better than logistic regression by providing the best AUC for showing the risk of cardiac death in adenosine myocardial perfusion SPECT patients.

ML Prediction of MACE

Betancur et al. led a study evaluating the added predictive value of integrating patient information with SPECT MPI to predict major adverse cardiovascular events (MACE) through utilization of a ML algorithm [16]. A supervised ML algorithm was utilized with logit-boost for this purpose. A total of 2619 patients were monitored for MACE while undergoing exercise or pharmacological stress with high-speed SPECT MPI [16]. The study included 28 clinical variables, 17 stress variables, and 25 imaging variables and these were recorded. In approximately 3 years follow-up, 239 patients had MACE events. Unsurprisingly, ML combined had superior MACE prediction than ML imaging (AUC: .81 vs .78, $p < .01$). The ML also had higher MACE predictive accuracy when compared with expert reader, automated stress total perfusion deficit, and automated ischemic perfusion deficit (AUC: 0.81 vs 0.65 vs 0.73 vs 0.71, $p < 0.01$ for all). The risk reclassification of the ML algorithm when compared to the expert reader was 26% ($p < .001$). Betancur et al. finally concluded that ML combined algorithm with clinical data had statistically significant higher accuracy for predicting 3-year MACE events in comparison to visual or automated perfusion assessment in SPECT MPI patients.

Automatic Mitral Valve Plane Localization in MPI

The precise location of the mitral valve plane during left ventricular segmentation for MPI SPECT frequently requires manual adjustment. As a result of this, this consequently affects the quantification of perfusion. Betancur et al. created a supervised learning algorithm for automatic mitral valve placement [17]. Betancur et al. conducted a study in 392 consecutive patients for stress and rest MPI SPECT [17]. These scans were used for training and validation. The ML derived algorithm had an AUC of 0.82 for identifying CAD in relation to 2 experts with AUC of 0.79 and 0.81 and unadjusted mitral valve plane with AUC of 0.63.

Use of Deep Learning ML in Nuclear Cardiology

The majority of ML utilization shown in previous studies have used supervised learning algorithms for prediction of various complications in CAD (Table 1). There are also limited studies showing the use of deep learning algorithms in CAD intervention. Betancur et al. led a multi-center study evaluating automatic prediction of CAD obstruction by myocardial perfusion imaging (MPI) implemented through deep learning in comparison to total perfusion deficit. Obstructive CAD was described as stenosis beyond 70% or 50% for the left main artery [18••]. The study contained 1638 patients without known CAD who underwent stress Tc-sestamibi or tetrofosmin MPI at 9 institutional sites [18••]. After MPI, invasive coronary artery angiography was performed within 6 months. The deep learning ML algorithm underwent extensive training with raw and quantitative polar maps. In the 1638 patients, only 1018 (62%) had obstructive CAD. Only 1797 coronary vessels among 4914 (37%) had obstructed CAD. Deep learning ML had a higher AUC than total perfusion deficit for CAD prediction (per patient: 0.80 vs 0.78; per vessel 0.76 vs 0.73: $p < .01$). Surprisingly, if the deep learning ML architecture matched the TPD specificity, per-patient sensitivity (79.8% to 82.3%, $p < .05$) and per vessel (64.4% to 69.8%, $p < .01$) sensitivity increased. The study clearly showed that deep learning ML had the ability to augment automatic interpretation of MP in comparison to contemporary methods.

Potential of Deep Learning ML in Nuclear Cardiology

Future studies should try to further implement the use of deep learning ML in nuclear cardiology. In contrast to supervised learning, deep learning learns in increments in a number of neuronal like layers [4]. Other ML algorithms reach their limits with large data sets but deep learning improves exponentially with large data sets. It can extract valuable information from heterogeneous data and predict cardiac death with great accuracy [4]. A recent innovation known as automated transform by manifold approximation (AUTOMAP) has the ability to reconstruct images from a variety of modalities such as PET scans [21]. No expert is needed. This can be particularly useful for reducing dose exposure in patients during SPECT and create high-quality images. Deep learning can improve the quality of perfusion SPECT images or representation of images on polar maps.

Table 1 Studies utilizing machine learning approaches in nuclear cardiology

Author	Number of patients	Age	Type of machine learning	Study description	Area under curve (AUC)
Arsanjan et al. [14]	713	62 ± 13* 66 ± 11#	Supervised learning	To predict revascularization	0.81 ± 0.02
Arsanjan et al. [13]	1181	64 ± 12* 48 ± 11#	Supervised learning	To predict coronary artery disease with integration of clinical information	0.81 ± 0.02
Betancur et al. [16]	2619	70 ± 12* 62 ± 11#	Supervised learning	To predict MACE	0.81 ± 0.03
Betancur et al. [17]	392	62.5 ± 9.9	Supervised learning	To determine mitral valve position during MPI	0.82 ± 0.08
Arsanjani et al. [12]	957	60 ± 12	Supervised learning	To predict coronary artery disease	0.92
Alonso et al. [15•]	8321	71 ± 12	Supervised learning	To predict cardiac death	0.83
Betancur et al. [18••]	1638	62.6 ± 11.7* 65.2 ± 11.0#	Deep learning	To compare automatic prediction of CAD in relation to total perfusion deficit	0.80 per patient 0.76 per vessel
Nakajima et al. [19]	1001	69 ± 10	Supervised learning	To test the diagnostic accuracy of ANN	0.91
Guner et al. [20]	308	57.5 ± 10.9* 57.9 ± 12.2#	Supervised learning	To detect coronary artery stenosis	0.74 images 0.65 gender and images 0.72 gender, images, and body mass index

*- stands for group 1

#- stands for group 2

Potential Limitation of ML in Nuclear Cardiology

Although ML's potential in nuclear cardiology is limitless and it will have an inevitable role in patient management, there are a number of issues which need to be resolved for successful implementation in clinical care. For ML algorithms to function properly and accurately, it requires extensive training with elaborate data sets. There are a number of difficulties in obtaining these data sets. First, the datasets must be de-identified and must be shared among institutions [4]. Secondly, for even sharing data sets, it requires multiple institutional review board approvals which can be a time-consuming process. If the large data sets can be publicly available, this can enable training of ML algorithms. This is particularly important for the deep learning subtype of ML.

Some form of a universal standard is necessary for data standardization. Although picture archiving and communications system (PACS) and digital imaging and communications in medicine (DICOM) are extremely useful for imaging data, there are a number of discrepancies between institutions. Each institution may have their own classification, follow their own protocols, or have different acquisition protocols [4]. Achieving a universal or similar coding process for data standardization is paramount in order to facilitate the growth of ML within nuclear cardiology in the future. .

Integrating patient information with imaging data is a valuable process for improving the accuracy of the ML architecture. However, clinical data from the EMR does not share the same interface as imaging software in many institutions. The manual entry of numerous pertinent medical information into the imaging or machine learning platforms can be a tedious process. Some form of easier data mining and sharing between these two interfaces can facilitate a seamless transition which can further advance machine learning training in institutions. Fortunately, the American Society of Nuclear Cardiology is consolidating patient information into an image guide registry, which will be quite helpful for all aspiring ML institutions [22].

Another key aspect of machine learning is that it is not adept at accepting change. If patient or imaging information previously stored but changes over time, it is difficult for the algorithm to accept [2]. Some form of external validation is necessary to facilitate the ML algorithm to recognize and incorporate change in patient or imaging information. The ML algorithm may need exposure to multi-center registries containing a wide variety of characteristics.

Future of ML in Nuclear Cardiology

The presence of ML will create a renaissance in the field of nuclear cardiology with positive effects in patient care for

years to come. The emergence of any innovation is not without its trials and tribulations. Our primary instinct is to welcome any development and evaluate its potential benefits in clinical care. Some may embrace its entry while others may be more hesitant. The evolution of nuclear cardiology is a dynamic process in which there are constant changes in techniques, tracers, and cameras [1]. Artificial intelligence is not a need but a necessity for the future of nuclear cardiology as the orbits of automatic quantification and ML become closer and closer. For machine learning to reach its full potential, several issues regarding validation, data sharing, legal, financial, and execution of a number of processes must be solved for successful implementation. The frontier of ML is a vast expanse which can benefit the medical community and patient care in the immediate future.

Compliance with Ethical Standards

Conflict of Interest Karthik Seetharam declares that he has no conflict of interest.

Sirish Shresthra declares that he has no conflict of interest.

James D. Mills declares that he has no conflict of interest.

Partho P. Sengupta is a consultant for HeartSciences, Ultromics, Kencor Health.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the mentioned authors.

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