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Review

Artificial Intelligence in Nuclear Cardiology

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Abstract: Background/Objectives: Artificial Intelligence (AI) is becoming increasingly important in Medicine. The aim of this review is to summarize its use in the field of Nuclear Cardiology. **Methods**: After a shrort description of how AI works, the main reported applications have been examined. **Results**: AI has been applied according to various approaches for diagnosis and prognosis. The achieved gains have been so far relatively limited as compared to the traditional methodologies. However, promising results have been reported, including interesting perspectives for their explainability. **Conclusions**: AI is going to play an important role soon in Nuclear Cardiology, but further improvements are needed, and several important issues must be solved, such as availability, explainability, liability, and ethics of its application in clinical decision making.

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1. Introduction: Artificial Intelligence in Medicine

Artificial Intelligence (AI) is increasingly transforming the landscape of medicine by providing advanced tools for disease detection, classification, and prognosis. At its core, AI refers to computer systems that can perform tasks typically requiring human intelligence, such as recognizing patterns, learning from experience, and making informed decisions. Among its most significant contributions to healthcare are its abilities to assist clinicians in diagnosing diseases, stratifying patients by disease severity, and predicting clinical outcomes with unprecedented speed and accuracy [1,2].

AI learns by analyzing vast amounts of data. In medicine, this typically involves medical images, electronic health records, genetic information, and clinical readouts. By processing these data, AI systems identify complex patterns and relationships that may be imperceptible to human observers. This learning process is achieved through algorithms that improve their performance over time as they are exposed to more examples—a process known as machine learning (ML) [3].

ML is a subset of AI that focuses on training algorithms to make predictions or decisions without being explicitly programmed for each specific task. Traditional ML models often require structured data and rely on manually engineered features to achieve optimal performance [4]. In contrast, deep learning (DL), a specialized branch of ML, leverages artificial neural networks inspired by the human brain. These networks are composed of multiple layers that enable the automatic extraction of hierarchical features from raw data, such as images or text, making DL particularly effective in tasks like medical imaging analysis [5].

The learning process typically involves dividing the available dataset into three distinct subsets: the training set, the validation set, and the test set [6]. The training set is used to teach the AI model by allowing it to recognize patterns and learn relationships within the data. The validation set helps fine-tune the model by evaluating its performance during training and adjusting parameters to prevent overfitting [7]. Finally, the test set is used to independently assess the model's generalization ability on previously unseen data. The performance of an AI model is often evaluated using various metrics, with the confusion matrix being a fundamental tool [8]. The confusion matrix provides a detailed breakdown of the model's predictions, including true positives, true negatives, false positives, and false negatives. This allows researchers to calculate important performance indicators such as accuracy, sensitivity, specificity, and precision—metrics that are critical in medical applications where diagnostic errors can have significant consequences [9].

The applications of AI in medicine are diverse and expanding rapidly. AI-powered algorithms are now employed to detect diseases such as cancer, cardiovascular conditions, and neurological disorders from imaging modalities like MRI, CT, and X-rays [10,11]. They assist in classifying disease severity, which supports treatment planning and risk stratification [12]. Furthermore, AI models can predict patient outcomes by analyzing historical and real-time data, contributing to personalized medicine and improving prognostic accuracy [13].

2. AI in Nuclear Cardiology

As regards nuclear cardiology, AI-based techniques have been extensively implemented in image acquisition and processing. The focus of this review, however, will be on AI applications for the interpretation of nuclear cardiology images and for their integration with other patient data for diagnostic and prognostic purposes.

Although AI is considered a quite recent development in the field of medicine in general, and of diagnostic imaging in particular, its use in the setting of nuclear cardiology techniques dates to many years ago. It was already in 1992 when Fujita and coworkers employed a neural network with the aim of helping the physician to detect abnormalities in ^{201}Tl myocardial perfusion single photon emission computed tomography (SPECT) polar maps. The neural network was trained with 58 polar maps coupled to their correct interpretation and then its classification in 16 further cases was compared with that proposed by unexperienced and experienced readers. The results showed a slight superiority over the unexperienced observer but remained inferior to those achieved by the experienced reader. As expected, increasing the complexity of the neural network and the number of training iterations improved the accuracy, but computing capabilities were then still a limitation in term of processing time [14]. The very modern approach of that paper was not followed by other similar experiences in the subsequent years.

At the beginning of this century, automation in image interpretation was performed by case-based reasoning. This method implies the construction of a case library of images interpreted by experienced readers; then, the individual study is compared with the library and the diagnostic interpretation is based on that of the five most similar cases. In the article by Khorsand and coworkers, the case-based reading was compared with the Cedar Sinai polar map analysis and with the visual interpretation by an experienced observer. The results of the three approaches were similar and no significant diagnostic gain was achieved [15].

Another approach dating back to the end of the last century was the knowledge-based expert system, in which a series of interpretative rules derived from the observer analysis of images with known diagnosis was used to classify the results of myocardial perfusion scans. In their comparative study, Garcia and coworkers could demonstrate that the expert system obtained a reasonable accuracy when the reference was the interpretation by an experienced nuclear physician, whilst the agreement was lower using coronary angiography as the gold standard. However, the human expert as well was less effective when compared with coronary angiography [16].

A further development of this approach by the same research group has been to construct an AI-driven structured report. As in previous studies, the reference standard was the consensus of experts. In the study by Garcia and coworkers, the AI-driven structured report was not inferior to the consensus expert reading only if the setting of high specificity was chosen. Otherwise, both in case of trade off sensitivity/specificity and of high sensitivity settings there were significant differences between AI-driven report and the reference standard, which were also clearly higher than those between an additional independent expert and the consensus reference [17].

The overall disappointing results of the above-mentioned approaches together with AI evolution opened the way to the extensive use of ML and DL based models for improving the interpretation of nuclear cardiology examinations. However, the first applications of ML to MPI in the diagnostic setting did not reach more effective results than those reported by case-based or knowledge-based methodologies. For instance, Arsanjani and coworkers enrolled more than one thousand patients and submitted their MPIs and some clinical data to a Logit-Boost ML algorithm to identify coronary artery disease (CAD). The achieved diagnostic accuracy was equal to that of one of the experts and just slightly superior to another observer, and to the usual TPD approach. In general, the differences among ML and the other classifications were less than 5% [18]. In another study, a direct comparison between DL-based and knowledge-based approaches was performed in the detection of MPI abnormalities, using as reference the interpretation by two experienced readers. The two approaches reached high levels of sensitivity, specificity, and accuracy, but it is notable that among various pretrained networks used for DL there were remarkable differences in the results [19].

Indeed, even these more advanced AI applications have potential pitfalls. A first important problem is the availability of adequate datasets, because in case of too small patient cohorts the results of training may be eventually very accurate, but just in the dataset itself, and useless in another population due to overfitting [20]. Other problems can be related to the definition of the reference standard. It is for instance interesting to compare two studies, which apparently performed a very similar analysis, respectively on 566 and 1007 polar maps. Although they used almost the same algorithms, the best accuracy achieved by ML was quite different, 76.5% versus 93%. One of the possible explanations is that in the former study the reference standard was coronary angiography, and several clinical features were included in the model, whilst in the latter it was the consensus of two experienced readers and just MPI parameters were considered [21,22]. A reasonable comment could be that the same AI approach can obtain quite different results if applied to different contexts and that it is thus difficult to define the true reliability of these new methodologies. Another problem can arise when there is a selection bias in the training population, for instance because of the prevalence of high-risk patients, which in turn can produce a disease overestimation in the testing cohort. To overcome this bias, data-augmentation techniques have been proposed, with the aim of rebalancing the case distribution in the training set to make it closer to the testing population. Miller and coworkers could thus achieve an improvement in the AI model classification over that obtained using the original population. However, it is quite disappointing to remark that the best AI classification after selection bias correction was just slightly better than that reached by the traditional TPD approach [23].

It is therefore clear that there is the need of a rigorous methodology for applying AI techniques to diagnostic imaging in the field of cardiology. A fundamental proposal for achieving the required level of methodological soundness is the PRIME checklist. This consensus statement identifies 7 sets of requirements to be fulfilled to ensure a correct use of ML models and to support a reliable description of models itself and of the achievable results. By reading the statement it is apparent that the application of AI to cardiological imaging is a complex issue, which requires a very demanding methodology [24].

A central role for the development of AI applications in nuclear cardiology has been played by the creation of a large registry of MPI scans acquired with CZT SPECT, the REFINE (Registry of Fast Myocardial Perfusion Imaging with Next generation SPECT) [25]. Using the data collected by REFINE several papers have explored the capabilities of different AI approaches.

The first purpose has been to improve the diagnosis of CAD using DL, as shown by the article by Betancur et al. [26]. Similarly, the same group applied AI to analyze the combination of upright and supine images acquired by CZT cameras. The results confirmed the superiority of this approach over the established TPD method [27].

A particular setting in which the use of AI could be advantageous for supporting the physician's choice is the interpretation of stress-only MPI. Liu and coworkers applied a deep convolution neural network to a very large population (37,243 patients) and demonstrated higher accuracy and specificity than the traditional defect size approach, although the sensitivity was slightly lower [28]. On the other hand, using ML Miller and coworkers tried to predict the pre-test probability of an abnormal MPI result in patients of the REFINE registry, considering 30 clinical features. The model was more effective than the standard ones, such as the Diamond-Forrester [29].

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Getting a significant superiority over traditional methods is the ultimate target of AI techniques, but another important goal to be reached is the implementation of explainability methods, which make possible for the physician and for the patient to understand how AI has classified the single study and consequently could improve the acceptance of AI derived clinical decisions. In their study using DL on a quite large set of patients, Otaki and coworkers provided both an attention polar map that highlighted the region deemed abnormal by DL and a CAD probability map conveyed in the established 17-segments AHA scheme. They reported that DL reached a significantly larger area under the curve (AUC) than the traditional TPD or the experienced reader, with the further advantages of an easy implementation in standard clinical software and of short calculation time [30].

Despite the large patient cohorts made possible by the REFINE, the final gain of AI models applied for diagnostic purposes over traditional methods has been always quite limited. A field in which the use of AI could be more effective is prognostication, since AI allows the combination of multiple parameters beyond the MPI polar maps. The REFINE has been the basis of various studies about prognosis. Hu and coworkers have explored the capability of ML to predict the occurrence of early revascularization in CAD patients. The ML used 18 clinical, 9 stress and 28 imaging variables and outperformed TPD and nuclear cardiologist expert interpretation. Moreover, even in this setting the Authors were able to provide a method for making explainable the ML classification [31].

A further step has been to use ML for MACE prediction. On a very large proportion of REFINE patients the Authors explored various ML methodologies and determined the most effective set of imaging and clinical variables to achieve a MACE prediction that was superior to those of stress TPD and of traditional multivariable models [32]. Although the best prediction was reached using the full variable panel, reduced and more practical models obtained clinical valuable results. Similarly, Betancur and coworkers explored the predictive value of ML in a cohort of 2619 patients and demonstrated that the ML combination of imaging and clinical features was superior to ML imaging alone, and to the other traditional methods [33]. These results were confirmed in a much larger patient cohort of over 20,000 patients by Singh and coworkers, who developed an explainable DL model for predicting MACE, which obtained an AUC of 0.73, compared with 0.70 of a logistic regression model and 0.65 of stress TPD [34]. The explainability of the patient classification is another major merit of this article. A most recent and intriguing paper about the potential of AI for prognostication has demonstrated that it is possible to identify patient clusters at higher risk for cardiovascular events even among MPI studies classified as normal [35]. This is as well a study based on the REFINE registry, which in the meantime has been updated to the REFINE 2.0 [36].

Other studies have explored the potential of AI approaches applied to myocardial positron emission tomography (PET). Juarez-Orozco and coworkers used quantitative PET data as reference to classify the patients as ischemic (regional myocardial perfusion reserve < 2.0) or as at high risk (global MPR < 2.0). Then they explored the capability of ML to predict these two PET classifications based on demographic, clinical and functional variables, achieving an acceptable AUC [37]. An interesting further step by the same group has been to use DL for MACE prognostication. They compared the predictive power of the DL approach with that of different traditional models (clinical, functional, absolute perfusion quantification, and of their integration). DL achieved the largest AUC (0.90), whilst the integrated approach reached 0.85 [38]. Singh and coworkers applied DL to 4735 patients submitted to ^{82}Rb PET obtaining an AUC of 0.82, compared with myocardial flow reserve (AUC = 0.70) and a comprehensive logistic regression model (AUC = 0.75) [39].

The usefulness of AI was also explored in the setting of other cardiological PET investigations. For instance, Kwiecinski and coworkers used 18F-NaF PET coupled with CT angiography and demonstrated that a ML model integrating clinical, CT plaque and 18F-NaF PET variables reached an AUC = 0.85 for predicting subsequent myocardial infarction [40].

Another field of potential applications of AI is the detection of cardiac uptake of bone tracers in patients with Transthyretin Amyloidosis (ATTR). In a first experience, Delbarre and coworkers used a convolutional neural network on a training set of more than 3,000 images and then on a validation set of 1,633 images, with very good results (AUC = 0.999) [41]. Similarly, quite effective results for

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detecting ATTR in bone scans performed for the usual indications were obtained by Halme and coworkers, who evaluated 1334 patients and demonstrated an AUC of > 0.85 for detecting ATTR uptake [42]. In a very complex study, Salimi and coworkers examined a ML model for ATTR detection and scoring, which performed quite well in the external datasets of patients suspicious of ATTR. On the other hand, in a further large dataset of patients screened for other indications the results were quite disappointing, with just ten suspicious cases detected and 4 of them reclassified as false positives by an expert review [43]. Better results have been reported by Spielvogel and coworkers, who examined a very large dataset (16,241 patients with 19,401 images). Their results were excellent for the diagnosis of cardiac ATTR, with very high AUC. Even for the screening task the results were satisfactory, with a very limited rate of false positive and false negative classifications. Moreover, a positive result achieved by the AI model showed a significant predictive value for the subsequent mortality and for heart failure hospitalizations [44]. DL has been effectively used to perform an automated quantification of 99mTc-PYP in patients with suspected ATTR submitted to SPECT [45].

Finally, it is worth mentioning the study by Togo and coworkers for applying convolutional neural network in the detection of cardiac sarcoidosis using [^{18}F]-FDG, obtaining a gain in comparison to the standard SUV based approaches [46].

3. Final Remarks and Perspectives

The great interest in AI applications to the field of cardiology is confirmed by the steady increase in articles reporting AI-based models for diagnosis and prognosis and nuclear cardiology is fully involved in this process. The multiple advantages of AI are well-known and include the capability of extracting hidden information both from images and patient characteristics, to handle big data, to integrate clinical and imaging features and to offer an objective basis for physician’s interpretation.

On the other hand, the current hype about AI should not let us neglect its current limitations and the problems related to its use. So far, the gains in terms of diagnostic accuracy remain relatively small. As for the prognostic uses, they appear more promising but there is still need of prospective confirmative studies. Moreover, the wide availability of the proposed algorithms for the common user is still far from being reached.

Other important issues that require to be solved are the protection of patient personal data, the cybersecurity of the programs, and the costs for their development and implementation.

The topic of result explainability is as well very important. It must be considered that the perception of explainability significance can be quite different in those who develop the model versus the physician, particularly if the latter should involve the patient in the comprehension of AI results that concern his/her management.

Finally, the ethical issue of how AI can be used for clinical decision making remains unsolved, including the legal liability for the ensuing decisions. In this last instance, it is still unsettled how the responsibility should be divided between AI (and its developers) and the physicians who use the AI-derived classification. All these issues could become even more complex with AI progress and the consequent expansion of its application fields.

Abbreviations

The following abbreviations are used in this manuscript:

AI	Artificial Intelligence
ATTR	Transthyretin Amyloidosis
AUC	Area Under Curve
CAD	Coronary Artery Disease
DL	Deep Learning
ML	Machine Learning
MPI	Myocardial Perfusion Imaging
PET	Positron Emission Tomography

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SPECT Single-Photon Emission Computed Tomography.

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