Journal of Cardiology 79 (2022) 319–325

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Review

Prospects for cardiovascular medicine using artificial intelligence

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ARTICLE INFO

Article history:
Received 7 October 2021
Accepted 19 October 2021
Available online 10 November 2021

Keywords:
Artificial intelligence
Cardiology
Deep learning

ABSTRACT

As the importance of artificial intelligence (AI) in the clinical setting increases, the need for clinicians to understand AI is also increasing. This review focuses on the fundamental principles of AI and the current state of cardiovascular AI. Various types of cardiovascular AI have been developed for evaluating examinations such as X-rays, electrocardiogram, echocardiography, computed tomography, and magnetic resonance imaging. Cardiovascular AI achieves high accuracy in diagnostic support and prognosis prediction. Furthermore, it can even detect abnormalities that were previously difficult for cardiologists to detect. Randomized controlled trials begin to be reported to verify the usefulness of cardiovascular AI. The day is approaching when cardiovascular AI will be commonly used in clinical practice. Various types of medical AI will be used for cardiovascular care; however, it will not replace medical doctors. We need to understand the strengths and weaknesses of medical AI so that cardiologists can effectively use AI to improve the medical care of patients.

Introduction

In recent years, AI has made remarkable progress, and various medical AI studies have been reported [1,2]. Many studies, in particular, are employing AI for image interpretation in the fields of radiology and pathology. In addition to diagnostic imaging, there have been reports of innovative AI studies, such as the use of neuroprosthesis for stroke patients using a brain–computer interface [3,4]. Many AI studies have been reported in the cardiovascular field as well [5]. Several types of AI are being developed for various examinations such as X-ray, electrocardiogram (ECG), echocardiography, computed tomography (CT), and magnetic resonance imaging (MRI) (Fig. 1). Karwath et al. developed an AI that uses machine learning techniques to detect heart failure patients who respond to beta-blockers [6]. Attia et al. reported an AI that predicts future paroxysmal atrial fibrillation with high accuracy from an ECG during sinus rhythm and an ECG AI, by which a decrease in left ventricular contractility can be determined [7,8]. Yao et al. conducted a randomized controlled trial on ECG AI and reported its utility in clinical practice [9]. The usage of ECG AI will be recommended in the medical practice guidelines once considerable evidence supporting its utility is available. The utility of detecting arrhythmia with wearable devices has already been reported; the Apple Watch, for example, has been approved as a medical device in Japan and its usage begins to increase [9].

Deep learning enables image recognition, and AI is said to have acquired "eyes." Currently, the development of "hands," "ears," and "mouths" in AI is in progress. There is competition around the world to develop robot arms that can hold objects as delicately as human hands. Engineers are working on "ears" and "mouths" that would enable smooth conversation through voice recognition and natural language processing. Smart speakers are about to work the same way as human "ears" and "mouths." If not only the "eyes" but also the "hands," "ears," and "mouths" of AI are developed, AI could be used in various medical fields. The importance of AI in clinical settings is increasing, and the need for clinicians to understand AI is also increasing. This review reports on the basic principles of AI and the current status and future prospects of the cardiovascular AI.

Basic knowledge of AI

AI is a broad concept that includes machine learning and deep learning. The concept of AI was proposed in 1956 and was defined as "the science and engineering of making intelligent machines" by John McCarthy. Machine learning is one part of AI, and deep learn-

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https://doi.org/10.1016/j.jjcc.2021.10.016
0914-5087/

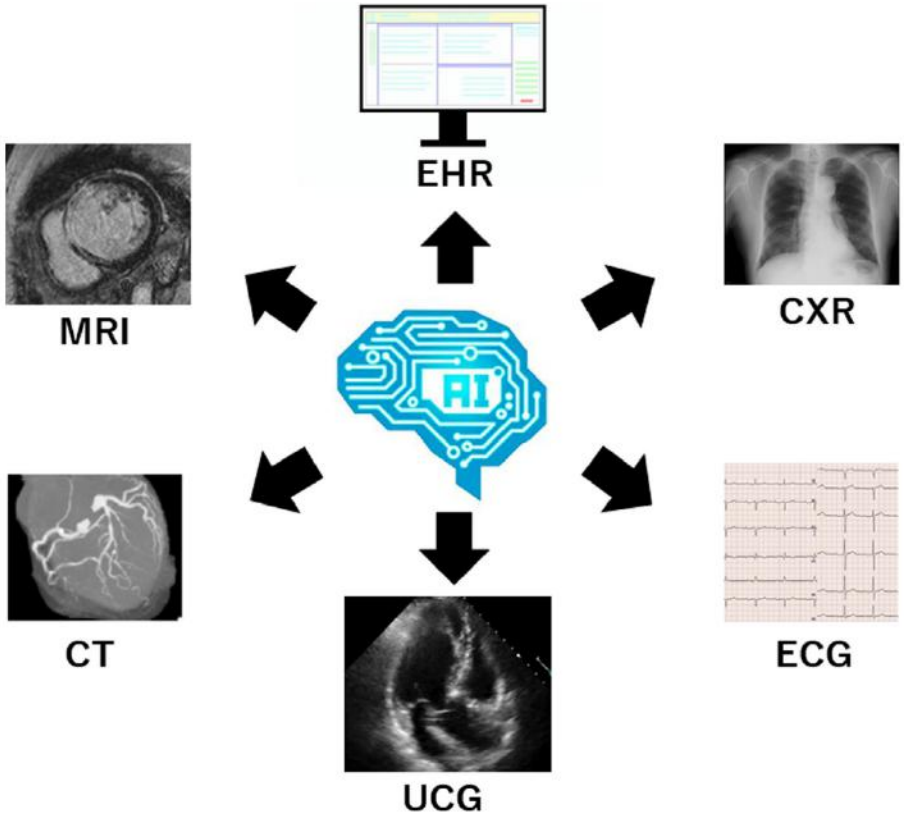

Fig. 1. *Artifical intelligence (AI) development status in the cardiovascular field.* AI for electronic health record (EHR), chest X-ray (CXR), electrocardiogram (ECG), ultrasound cardiography (UCG), computed tomography (CT), and magnetic resonance imaging (MRI) has been developed.

ing is one part of machine learning (Fig. 2). In recent years, deep learning has been attracting attention among AI researchers. Machine learning can be classified into three types: supervised learning, unsupervised learning, and reinforcement learning. Supervised learning is a learning method with a set of *data* and *correct answers* and is used for tasks such as image interpretation. Unsupervised learning is a learning method that does not require a *correct answer*; methods such as clustering analyze data trends. Reinforcement learning is the method used in “AlphaGo,” which won the world championship of Go. In reinforcement learning, by providing a reward for the AI action result, the behavior pattern that maximizes the reward is autonomously learned. Reinforcement learning can enable creation of AI that performs best in a specific environment.

In recent years, deep learning has been attracting particular attention in machine learning. Neural networks, which are the bases of deep learning, are the models that imitate the neural circuits in the human brain [10]. The neural network structure comprises three layers: an input layer for data input, a hidden layer (or intermediate layer) for processing the weights flowing from the input layer, and an output layer for outputting the result (Fig. 3). Deep learning is a model that improves accuracy by increasing the number of hidden layers in neural networks [11]. Increasing the number of hidden layers enables handling complex data. Various data characteristics have to be specified in conventional machine learning, while in deep learning, the machine can automatically extract the data characteristics from the given data. Deep learning enables high-performance recognition that was not possible with manually operated machine learning. Considerable advances have been made in recent years in the application of deep learning for image recognition. A convolutional neural network (CNN) is the standard for image recognition [12]. CNNs enable region-based feature extraction and build networks that respond to important visual inputs in the same manner as the visual cortex of animals. Deep learning of dynamic and static images is gaining popularity. Furthermore, new deep learning methods such as generative adversarial network (GAN) and transfer learning are being developed and applied to the medical field [13,14]. Bidirectional encoder representations from transformers (BERT) and Generative Pre-trained Transformer 3, AIs that interpret natural language, have been developed, and language AI as a topic is drawing researchers' attention [15,16]. There are unresolved issues such as ethical issues with regard to AI use and legal issues with regard to responsible use of AI. Technological innovation in the field of AI is progressing rapidly and will be applied to the medical field as well.

X-ray AI research

Chest X-ray examination is one of the most frequently used examinations in the cardiovascular clinical practice. Kermany et al. reported the use of X-ray AI for detecting pneumonia [17]. Using actual examples such as chest X-rays, they validated that transfer learning is useful in the medical field for detecting pneumonia. Transfer learning is a method of applying a model learned in one area to another area (Fig. 4). They first created an AI model using data (ImageNet) that contain hand-annotated 12 million images [18]. When the created AI model was further trained using X-rays of 5232 cases to create an AI for detecting pneumonia, the obtained results were good, with the area under the curve (AUC) of 0.97, sensitivity of 93.2%, and specificity of 90.1%. Lu et al. reported that AI could predict the prognosis only from chest X-rays [19]. A prognosis model was created using chest X-rays of 52,320 cases, and the mortality risk was classified into five groups: very low, low, moderate, high, and very high. The background-adjusted

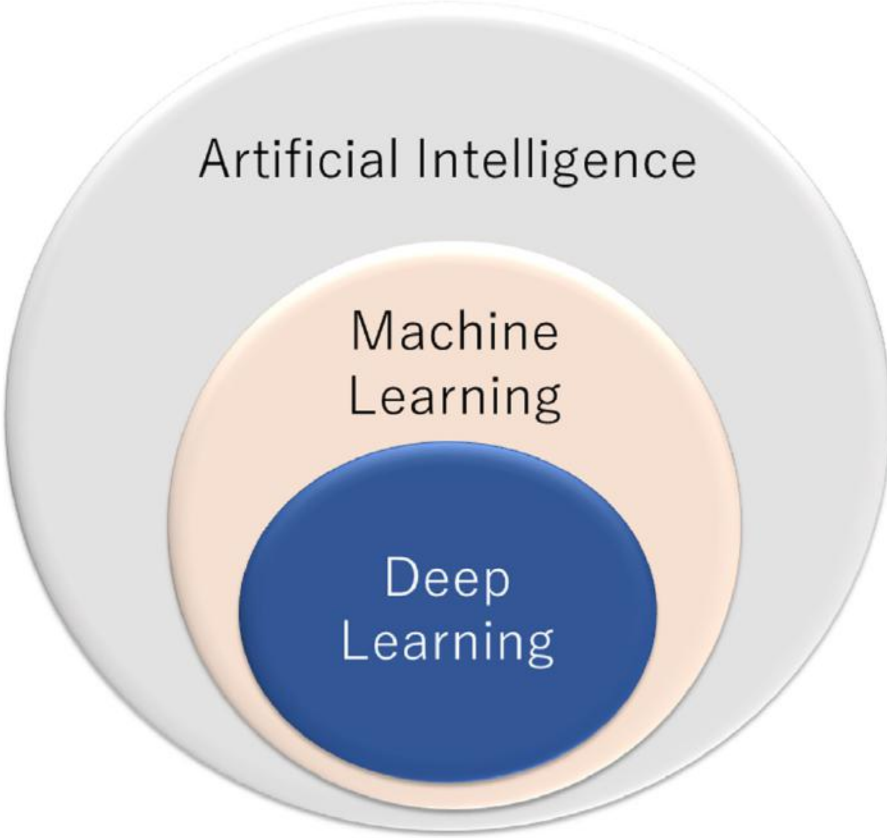

Fig. 2. *Artifical intelligence classification.* The relationship between artificial intelligence, machine learning, and deep learning.

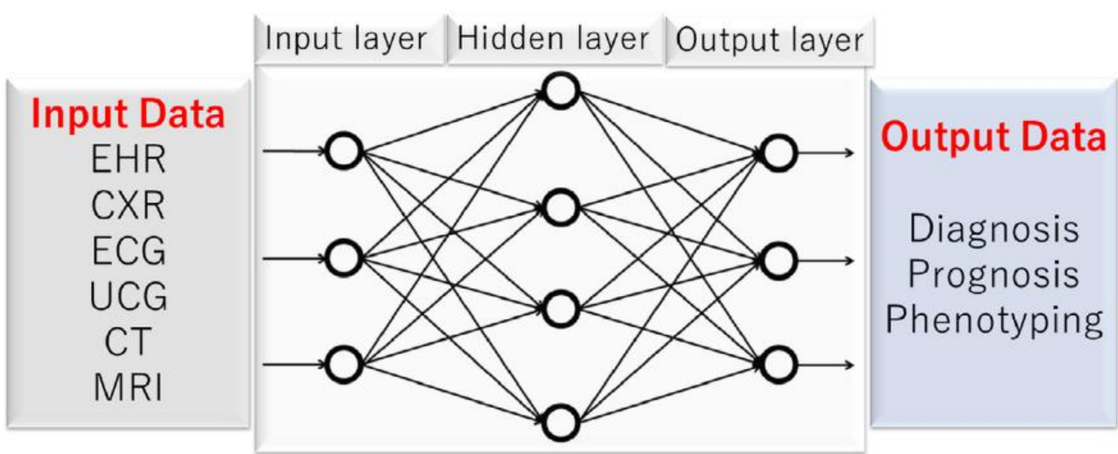

Fig. 3. *Neural network architecture.* Each neuron is a computational unit. A neural network comprises one input layer, multiple hidden layers (one hidden layer in the figure), and one output layer. In cardiovascular artificial intelligence, input data include electronic health record (EHR), chest X-ray (CXR), electrocardiogram (ECG), ultrasound cardiography (UCG), computed tomography (CT), and magnetic resonance imaging (MRI). The output data include diagnosis, prognosis, and phenotyping.

hazard mortality ratios were 1, 1.4, 1.7, 2.6, and 4.8 respectively, indicating that the prognosis can be predicted only from chest X-rays using AI. Toba et al. developed the AI that presumes hemodynamics based on chest X-ray data using X-rays of 657 patients with congenital heart disease [20]. The correlation coefficient between the pulmonary and systemic flow ratio measured via a catheter and that derived using AI from the X-ray data was 0.68. For the detection of a high pulmonary to systemic flow ratio, X-ray data-assisted AI was highly accurate, with the AUC of 0.88, whereas the AUC was 0.78 for the experts. Matsumoto et al. created an AI to discriminate heart failure from normal using chest X-ray images [21]. By transfer learning using VGG16 learned via ImageNet, an AI was created to distinguish heart failure from normal in 638 chest X-rays, and its accuracy rate was 82%. Sensitivity and specificity were 75% and 94%, respectively.

ECG AI research

ECG is a noninvasive and simple test that is frequently used in cardiovascular practice. Automatic interpretation of ECG has been frequently used in daily clinical practice for a long time, and automatic diagnoses of arrhythmia and ST abnormality can already be obtained. ECG AI may identify abnormalities that previously seemed difficult to be automatically identified. Attia et al. reported

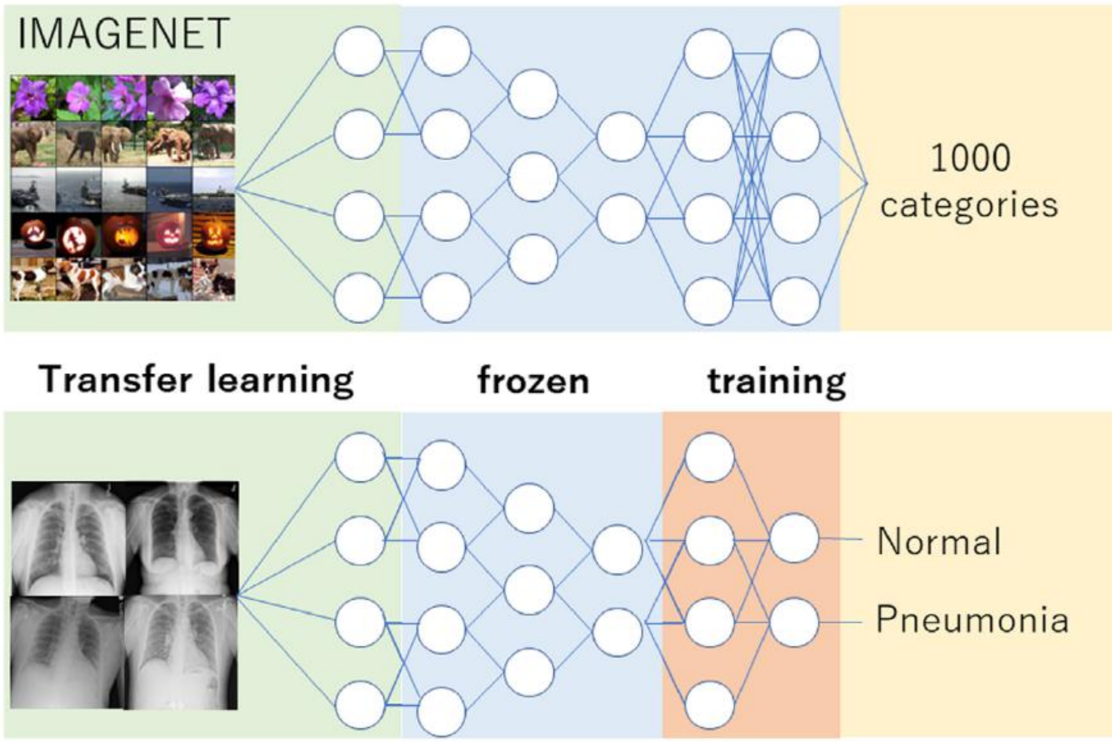

Fig. 4. *X-ray classification using transfer learning.* Transfer learning using the upper architecture representing a standard convolutional neural network model trained on a large dataset (ImageNet) and the transferred knowledge frozen by the weights of the new model [17]. Other layers will be retrained with X-ray data to allow new classification.

that ECG AI predicted the onset of atrial fibrillation during sinus rhythm [7]. When the onset of atrial fibrillation was predicted using ECG AI from the ECGs of 180,922 cases, the AUC was 0.87, sensitivity was 79%, and specificity was 79.5%, at which clinicians were surprised. Moreover, Attia et al. detected a decrease in ejection fraction (EF) using ECG AI from the ECGs of 44,959 patients to show that the AUC was 0.93, sensitivity was 86.3%, and specificity was 85.7% [7]. Yao et al. tested the effectiveness of ECG AI to detect EF reduction in a randomized controlled trial [9]. They assigned 22,641 cases to groups (with and without ECG AI) by cluster randomization to compare the diagnostic rate for determining EF reduction. In the group using ECG AI, the detection rate of EF reduction increased by ~30%. Goto et al. developed an ECG AI for diagnosing cardiac amyloidosis [22]. In the model created using ECG data of 3191 cases, the performance was good, with the AUC of 0.91. They also reported an improvement in the AUC to 0.96 when this method was combined with echocardiography. Sawano et al. developed an AI using the ECG data of 29,859 cases and detected aortic regurgitation with a high AUC of 0.80 [23]. Taken together, the development of ECG AI has progressed rapidly in recent years.

Echocardiography AI research

Echocardiography is a test from which plentiful dynamic information about the heart can be obtained, therefore, it is essential for cardiovascular care. In recent years, automatic cardiac function measurement, disease diagnosis, and prognosis prediction with echocardiography AI have been rapidly developing (Fig. 5). EchoNet-Dynamic is an automatic echocardiography AI developed by Ouyang et al. that is the focus of considerable attention [24]. With a three-dimensional (3D) CNN and semantic segmentation, based on 10,030 echocardiographic videos for training, they developed the AI that can be used to automatically measure the value of EF. The correlation coefficient between the EF value presumed by the AI and that determined by echocardiography specialists was as high as 0.9, which exhibited the AUC of 0.97. Salte et al. developed the AI that measures global longitudinal strain from an echocardiographic video [25]. The correlation coefficient between the actual measured global longitudinal strain and the presumed global longitudinal strain of AI was as high as 0.93, suggesting that AI could shorten the examination time for echocardiography. Katsushika et al. developed the AI that detects cardiac sarcoidosis with the AUC of 0.84 and an accuracy as high as that of a specialist, using 300 echocardiographic videos [26], suggesting that the echocardiography AI for rare diseases such as cardiac sarcoidosis could be created using transfer learning. Ulloa Cerna et al. have developed a highly accurate AI for predicting the 1-year prognosis (AUC 0.83), based on echocardiographic videos of 32,362 people [27]. Cardiologists assisted by the model substantially improved the predictive sensitivity by 13% when predicting survival one year later from the echocardiographic video. Shad et al. developed the AI that predicts postoperative right heart failure from preoperative echocardiographic video [28], whose prediction performance showed an AUC of 0.73, which was higher than that for the clinical expert team with the AUC of 0.58.

AI research on CT

Coronary CT can be used to evaluate the coronary arteries with minimal invasiveness. Many types of CT AI using analysis methods such as 3D-CNN have been developed. Martin et al. reported that CT fractional flow reserve (FFR) estimated using AI was useful for predicting revascularization and major adverse cardiac events (MACEs) [29]. The CT FFR of 159 cases estimated using AI could predict the onset of revascularization and MACE one year later with higher accuracy compared with conventional coronary CT angiography (odds ratio 3.4). Zeleznik et al. developed the AI that evaluates coronary artery calcification scores from plain CT and predicts cardiovascular events [30]. The AI evaluated the calcification score of the coronary arteries from plain CT (without contrast)

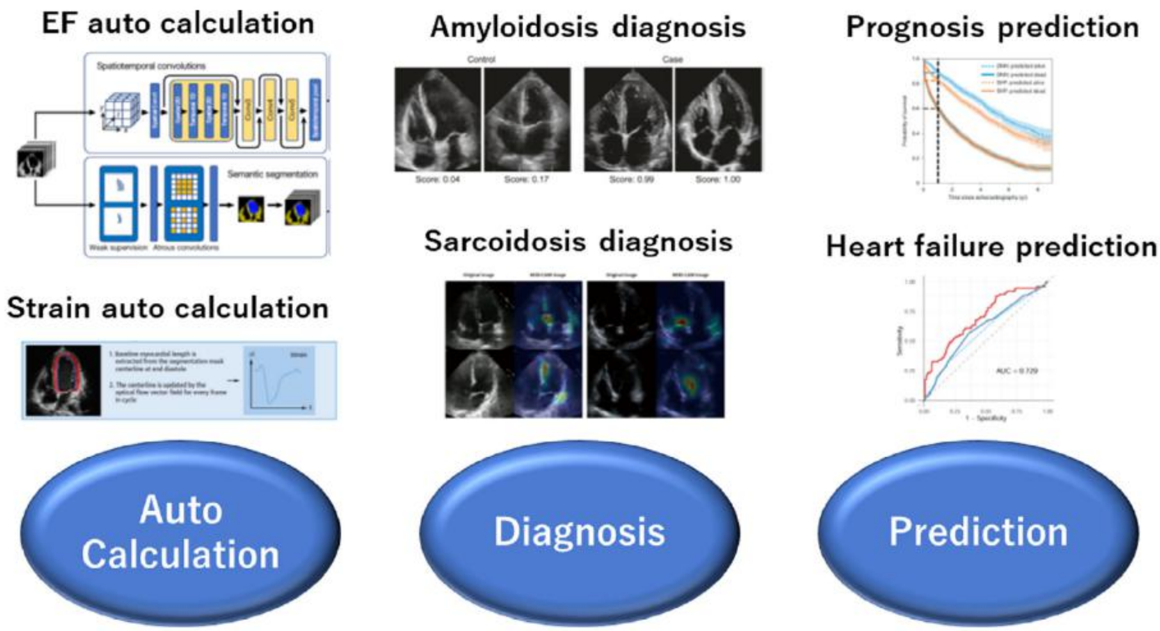

Fig. 5. *Application of artificial intelligence (AI) to echocardiography.* AI can be applied to automatic calculations, diagnoses, and predictions regarding echocardiography [22,24–28]. EF, ejection fraction.

of 20,084 cases. Between the measured value of the specialist and the estimated value of AI, the Spearman correlation coefficient was 0.92. AI-based calcification score assessment was useful for predicting prognosis for cardiovascular events (hazard ratio 4.3). Kumamaru et al. developed the AI that calculates FFR from coronary CT [31]. Using the coronary CT data of 921 cases, the features of the coronary artery were first extracted from CT data using GAN. Next, using the CT data of 131 cases, they created an AI capable of fully automatic estimation of the FFR value. Automatic estimation of FFR by CT AI could detect abnormal FFR with the AUC of 0.78, sensitivity of 84.6%, and specificity of 62.6%.

MRI AI research

Cardiac MRI is a highly useful test for evaluating the condition of the heart. Because some MRI data are open to the public, multiple MRI AIs have been created. Knott et al. predicted cardiovascular events using the AI that automatically estimates myocardial blood flow [32]. Myocardial perfusion reserve was evaluated using cardiac MRI data of 1049 cases of ischemic heart disease, indicating the utility of MRI AI in prognosis of cardiovascular events (hazard ratio 2.7). Zhang et al. developed a model for detecting old myocardial infarction in noncontrast cine MRI [33]. They created an AI to detect old myocardial infarction from cine MRI using late gadlinium enhancement data as the correct answer label and applied it to 299 patients who underwent contrast MRI of the heart. Old myocardial infarction could be detected with a high accuracy of 99%. Piccini et al. developed an AI to mimic expert image quality assessment of cardiac MRI image using cardiac MRIs of 424 cases [34]. Regression performance of this AI was in very good agreement with the human expert.

Cardiovascular AI using GAN

GAN is a technique for creating fake images, which generates nonexistent images using the learned data [13]. GAN comprises two networks, generator (generation network) and discriminator (discrimination network), and the quality of images can be improved by competing these networks with each other. In recent years, GAN has been used in developing cardiovascular AI. Miyoshi et al. created the AI that interprets neointimal coverage grade and yellow color grade from images of 47 cases of angioscopy [35]. The AI reading accuracy improved from the AUC of 0.77 to 0.81 when vascular endoscopy data were supplemented with GAN. Diller et al. used GAN to generate 100,000 cardiac MRI images from 303 cases with congenital heart disease [36]. All the MRI images generated by GAN were valid, according to the expert's interpretation. GAN can be useful for the image generation of rare diseases. Schutte et al. used Style-GAN to visualize what AI learned [37]. Pathological images of cancer were learned, and Style-GAN was used to generate images with a gradual change in malignancy from 0 to 1. From the generated images, one can visualize what AI has learned.

Ethics for medical AI

There are several examples of potential improper use of AI, such as collecting information for commercial purposes or monitoring personal behavior without consent. Additionally, it has been pointed out that even if there is no malicious intent, some uses of limited, low-quality, nonrepresentative data for AI analysis might result in deepening prejudice and disparity. Ethics is important in medical AI development. Jobin et al. reported that ensuring transparency, justice, nonmaleficence, responsibility, and privacy is important in the ethics for medical AI [38]. The World Health Organization has enumerated the following six principles in ethics for AI (Table 1): ① protecting human autonomy; ② promoting human well-being and safety and the public interest; ③ ensuring transparency, explainability, and intelligibility; ④ fostering responsibility and accountability; ⑤ ensuring inclusiveness and equity; and ⑥ promoting AI that is responsive and sustainable [39]. Rogers et al. reported the need to introduce patient and public perspectives for the development of medical AI [40]. Moreover, they reported that it is necessary to consider how medical AI will affect medical doctor–patient relationships.

Cardiologists learn deep learning programming

In general, many medical doctors feel that deep learning programming is difficult. However, programming languages are just

Table 1
Ethics in artificial intelligence.

	Item	Content
1	Protecting human autonomy	Humans should remain in control of healthcare systems and medical decisions.
2	Promoting human well-being and safety and public interest	The designers of artificial intelligence (AI) technologies should satisfy regulatory requirements for safety, accuracy, and efficacy for well-defined use cases or indications.
3	Ensuring transparency, explainability, and intelligibility	Transparency necessitates the publication or documentation of sufficient information prior to the design or implementation of an AI technology.
4	Fostering responsibility and accountability	It is the responsibility of stakeholders to ensure that AI technologies are used under appropriate conditions and by appropriately trained people.
5	Ensuring inclusiveness and equity	Inclusiveness requires that AI for health must be designed to encourage the widest possible equitable use and access, irrespective of age, sex, gender,income, race, ethnicity, sexual orientation, ability or other characteristics protected under human rights codes.
6	Promoting AI that is responsive and sustainable	Developers should continuously and transparently assess AI applications during actual use to determine whether AI responds adequately and appropriately to expectations and requirements.

languages, and like foreign languages, medical doctors can learn the basic usage in a relatively short time. Professor Yutaka Matsuo of the Faculty of Engineering, The University of Tokyo, who is famous in the field of AI, pointed out that medical doctors can learn programming language quickly. After learning the basic usage of programming, medical doctors can develop thier own AI by learning analytical know-how from websites whose communities engage in AI analysis competitively, such as Kaggle. It is difficult for medical doctors to obtain medical AI approval on their own; however, medical AI prototypes can be created by medical doctors without the assistance of engineers. Cardiologists are expected to understand the realities of AI research for using AI clinically in the future. When creating teacher data, it is critical to monitor how AI performance changes as the teacher data change. Additionally, it is important to know through AI research that AI is vulnerable to unknown data and unexpected noise. To utilize AI in daily clinical practice, medical doctors should be actively involved in AI research.

Future perspective

It is anticipated that AI for diagnosis (including wearable devices) in cardiovascular medicine will be dramatically developed in the future. Although various types of medical AI for cardiovascular care have been developed, they never eliminate the requirement of medical doctors. In Japan, the medical doctor bears the ultimate responsibility for patients' care, therefore, the role of medical AI remains to assist the medical doctor. Although several types of medical AI for diagnosis have been developed, the development of AI for treatment is limited. As for the medical treatment, randomized controlled trials, rather than AI predictions, are the gold standard for determining the best treatment protocols for specific conditions. Physicians will continue to play a major role in determining the best treatment for each patient in the future. On the other hand, medical doctors should make use of AI for the better diagnosis. Most importantly, AI could easily misdiagnose the target images whose characteristics are different from those of the image dataset to be learned by AI in the training step. Thus, the medical doctors who utilize the AI should know that AI is vulnerable to unknown data. If medical doctors firmly grasp the weaknesses of AI and utilize AI for diagnosis, improvement in diagnostic accuracy can be expected. Finally, from a questionnaire survey of 1041 radiologists and residents, Huisman et al. reported that limited levels of knowledge on AI are associated with fear of replacement, while intermediate-to-advanced levels of knowledge on AI are associated with a positive attitude towards AI [41]. As cardiologists have more knowledge on AI, they will increasingly be in favor of the use of AI and can make more effective use of AI in clinical practice.

Conclusions

Various studies on the use of cardiovascular AI in diagnostic techniques such as X-rays, ECGs, echocardiography, CT, and MRI have been reported. Medical AI is advancing rapidly, and different medical AIs are being developed for cardiovascular care; however, medical AI cannot fully replace the work of medical doctors. With the better understanding of medical AI, we as cardiologists will be better able to make effective use of AI and improve the medical care of patients.

Funding

None

Disclosure

The authors declare that they have no conflicts of interest.

Acknowledgments

We thank Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

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