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Applications of artificial intelligence in cardiovascular imaging

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Abstract | Research into artificial intelligence (AI) has made tremendous progress over the past decade. In particular, the AI-powered analysis of images and signals has reached human-level performance in many applications owing to the efficiency of modern machine learning methods, in particular deep learning using convolutional neural networks. Research into the application of AI to medical imaging is now very active, especially in the field of cardiovascular imaging because of the challenges associated with acquiring and analysing images of this dynamic organ. In this Review, we discuss the clinical questions in cardiovascular imaging that AI can be used to address and the principal methodological AI approaches that have been developed to solve the related image analysis problems. Some approaches are purely data-driven and rely mainly on statistical associations, whereas others integrate anatomical and physiological information through additional statistical, geometric and biophysical models of the human heart. In a structured manner, we provide representative examples of each of these approaches, with particular attention to the underlying computational imaging challenges. Finally, we discuss the remaining limitations of AI approaches in cardiovascular imaging (such as generalizability and explainability) and how they can be overcome.

Artificial intelligence
(AI). In general, algorithms that mimic human intelligence; in this article, algorithms that interpret medical images and data to assist the diagnosis, prognosis and therapy of cardiovascular diseases.

Deep learning
Machine learning with artificial neural networks that have a large number of hidden layers.

Features
Distinctive attributes of an image or a signal.

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Artificial intelligence (AI) is now ubiquitous and is applied in many sectors. Research into the use of AI in health care is one of the most active areas, and AI has already achieved impressive results. These successes have mainly been achieved in medical image analysis and signal processing. This achievement can be explained by the fact that the most prominent AI tool currently being used is deep learning, which is highly efficient at extracting spatial and temporal associations from large databases[1]. To do so, deep learning automatically extracts the most important image or signal features, which removes the need to select them beforehand through manual procedures. This revolution in image and signal processing occurred due to the use of convolutional neural networks, which enable the extraction of these optimal features spatially or temporally through convolutional operations that use a restricted number of parameters, thereby requiring fewer data for training than traditional fully connected neural networks[2].

Cardiovascular imaging is one of the most active clinical applications of AI[3,4] because of the challenges associated with processing images of a beating organ[5,6]. AI has been applied to all medical imaging modalities[7], from 2D and 3D images to temporal sequences[8] derived from cardiac MRI[9,10], CT[11], nuclear imaging[3] or ultrasonography[12,13]. Novel imaging modalities, such as electrocardiographic imaging, can also benefit greatly from AI[14–16]. The field of AI in cardiovascular imaging has been boosted by the availability of several publicly accessible image databases such as CAMUS, Kaggle, STACOM and UK Biobank[17].

Many different aspects of cardiovascular imaging can be improved by AI, starting with patient selection and referral, to learn which patients can benefit most from imaging and with the use of which modality[18]. Large screening databases can then be used to facilitate the detection of anomalies, as achieved by the use of electrocardiograms to diagnose heart failure[19]. AI can also facilitate diagnoses by learning the different imaging features associated with a given pathology[20,21]. Using follow-up data, AI tools can be built to predict the evolution of pathology and patient prognosis[22]. Finally, AI can also be used for therapy selection, planning, guidance and follow-up[23–25]. However, many challenges still need to be addressed to obtain AI methods that can be translated into clinical practice. One of the major problems is that AI learns specific patterns from a given training database, possibly limiting the generalizability of its performance to images of different quality or to rare diseases or manifestations.

In this Review, we discuss the different applications of AI in cardiovascular imaging and show how pre-existing

Key points

- Artificial intelligence (AI) algorithms have shown impressive results in specific and often time-consuming cardiovascular imaging tasks such as image segmentation, anomaly detection and patient selection; however, these applications are limited to specific tasks in the clinical workflow.
- In cardiovascular imaging, AI algorithms are often purely data-driven but can be improved when associated with biophysical models of the heart, which enables the integration of pre-existing knowledge of human anatomy and physiology.
- A bottleneck in AI applications often lies in the collection of imaging data and their annotation by experts, which is limited by the lack of resources and expertise; therefore, the creation of large databases must be a community effort.
- The appropriate integration of AI algorithms into clinical workflows remains an unresolved problem; important security, privacy and explainability issues must be resolved to achieve a sufficiently high level of trust.
- AI algorithms have the potential to enrich the amount and the robustness of information extracted from cardiac images, while at the same time redistributing physician time and work towards patient interaction and complex decision-making tasks.

Convolutional neural networks
Artificial neural network using convolution operations to compute features within its layers.

Convolution operations
The weighted sum of neighbouring pixel values in an image.

Generalizability
The ability of a machine learning algorithm to perform sufficiently well on a new data set unseen during the training stage; also known as robustness.

Biophysical modelling
Mathematical representation of biological phenomena using methods from physics.

Machine learning
The capacity of an algorithm to solve a task by exploiting training examples, instead of following predefined explicit instructions.

Accuracy
Measurement of agreement between the algorithm prediction and the expected result.

Supervised learning
Learning process using user-defined annotations on a training data set.

Ground truth
Data corresponding to the expected result of an algorithm.

Image segmentation
Specifying regions with labels in a medical image.

clinical knowledge can be included in AI methods to increase their robustness. We start by presenting important concepts in AI and the image computing tasks that can currently be performed by AI algorithms. These AI concepts and imaging computing tasks are parallel to the imaging modalities and cardiac pathologies (FIG. 1). Next, we present how knowledge of anatomy and physiology can be introduced into AI applications through biophysical modelling. Finally, we discuss the remaining challenges to the widespread use of AI in cardiovascular imaging.

AI concepts

AI has been used for >20 years in medical imaging[26], contributing to the development of computer-aided diagnosis, therapy and guidance solutions to assist clinicians. Machine learning has revolutionized the development of those solutions by exploiting statistical information extracted from previously acquired data sets to improve their performance. Indeed, machine learning algorithms rely on training data to learn the parameters of a given task, often complemented by validation data[27] to optimize those parameters. The accuracy of the learned task is then evaluated using test data, unseen during the previous learning stages.

Supervised learning[27] is a widely applicable technique in medical imaging, in which both input information (such as cine MRI) and output information (such as the ejection fraction of the left ventricle), considered to be ground truth data, are provided to the machine learning algorithm in the training data in order to learn a mapping from input to output information (FIG. 2). For medical images, the input often consists of a set of 2D or 3D (volumetric) images or even time series of 2D or 3D images, sometimes augmented with clinical information (such as patient age, sex or body mass)[28] as well as, in some cases, with cardiac biosignals (such as the electrocardiogram) and biological data. The learned output is specific to the medical task and can correspond to a set of quantitative metrics (such as ejection fraction values), in which case, it is called a regression problem[27], or to a set of discrete labels (such as the classes of cardiac pathology), in which case, it is called a classification problem. More sophisticated types of output data can be learned such as tissue labelling of image voxels in image segmentation problems, the displacement or velocity fields in image registration and motion analysis problems, or the bounding boxes around anatomical or pathological structures in image detection problems.

A common pitfall of machine learning methods is overfitting the training data, in which the algorithm performs far better on training data than on test data, thereby showing poor generalizability to unseen data sets and therefore an unreliable performance. Accordingly, the appropriate selection of training data is of utmost importance. Creating a training data set for supervised machine learning algorithms requires the generation of ground-truth output data associated with a set of medical images. The output data to be learned, called image annotations when they are solely related to the image content (for example, image labels, landmarks or tissue masks), are often created manually by medical experts. This process is usually time consuming when dealing

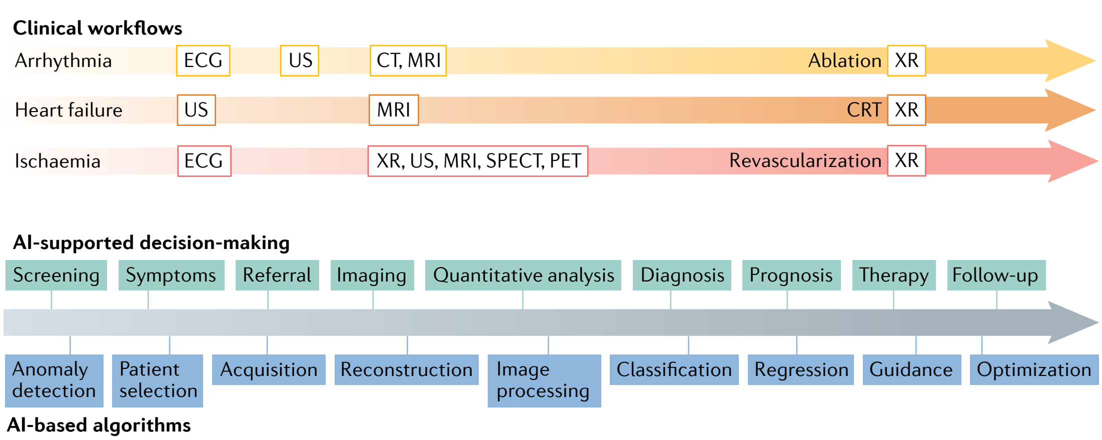

Fig. 1 | **Clinical workflow, AI-based algorithms and AI-supported decision-making.** A patient's pathway through the clinical workflow often includes the acquisition of a number of cardiovascular images with the use of various imaging modalities. Artificial intelligence (AI) can contribute to many of the required steps to acquire, reconstruct and process these images to achieve AI-supported decision-making. CRT, cardiac resynchronization therapy; ECG, electrocardiogram; SPECT, single-photon emission CT; US, ultrasonography, XR, radiography.

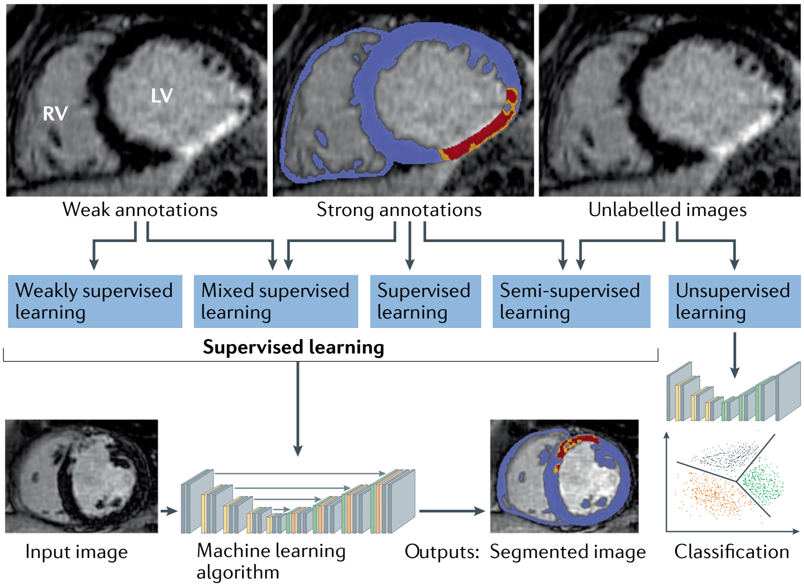

Fig. 2 | **Approaches to machine learning in cardiovascular imaging.** Different forms of supervision can be applied to machine learning algorithms to segment images of the left ventricle (LV) or to group images into clusters. Depending on the type of image annotations available (weak or strong), five different learning approaches can be devised. Four of these approaches are supervised (weakly, mixed, regular or semi-supervised) and the other is unsupervised in the absence of any image annotations. RV, right ventricle.

Image registration
Geometric transformation of an image to align it on another image.

Motion analysis
Computation and analysis of apparent displacements from time series of images.

Overfitting
When an algorithm is adjusted too closely to the training data during learning at the expense of generalizability to new data.

Image annotations
User-defined information associated with the input data.

Unsupervised learning
Learning process without user-defined annotations.

Transfer learning
Adjustment of a machine learning algorithm from one task to another.

Artificial neural networks
Algorithm mapping input to output data, involving multiple layers of non-linear computations.

Cost function
Criterion to be minimized during the training phase of machine learning algorithms.

with complex output data such as the delineation of cardiac structures in 3D images[29]. Another difficulty with supervised learning is related to the intra-observer and inter-observer variability, which can require the pooling of annotations from several experts. These limitations are why supervised learning is not easily applicable to large databases, for which other forms of supervision of machine learning algorithms have been developed[30].

In unsupervised learning[27], in which only input data are used without any additional annotation, the objective is to discover the underlying structure and patterns of the training data. For example, one might seek to find a low-dimensional description of the training set that can represent the observed data well or to categorize the data into clusters that might be correlated with clinical findings. In practice, unsupervised learning consists of testing several hypotheses about the structure of the data and keeping the ones that best explain the training set. To compensate for the lack of supervision, large amounts of data are usually required.

Between supervised and unsupervised learning lie several hybrid supervision methods of machine learning algorithms such as semi-supervised learning, in which only a subset of the input data has an associated output. Another way to alleviate the need for complex image annotations is to resort to weakly supervised learning, in which inexpensive but less informative annotations are provided instead of more expensive but explanatory output data. Similarly, mixed supervised learning combines a few strong annotations with many weak ones to decrease the cost of creating output content[31].

Finally, another common approach is transfer learning, in which one seeks to take advantage of an existing machine learning algorithm created to solve a previous problem in order to solve a different but related problem[30]. This approach is useful to adapt a machine learning algorithm to changes in the input data (such as cardiac images originating from a different MRI scanner) or in the output task (such as solving a segmentation problem instead of a detection problem).

Independently of the type of supervision, machine learning algorithms rely on statistical methods that make some generic hypotheses about the structure of input data or the mapping between input and output[32]. Among them, deep learning methods[2,33] and, more precisely, convolutional neural networks have had a considerable effect on the analysis of medical images, often outperforming previously developed machine learning approaches[34]. Deep learning methods are built as multiple layers of connected artificial neural networks that gradually map input data into output data through complex non-linear relationships. The training of these convolutional neural networks consists of minimizing a cost function that measures the discrepancy between the output of the network and the ground truth (in the case of supervision) or by a mathematical model. Among the most popular neural networks used in medical image analysis, the U-Net[35] is a convolutional neural network suitable for solving segmentation problems on whole images, Generative Adversarial Networks[36] generate synthetic images, whereas deep variational autoencoders create a compact statistical description of the training data[37]. Deep learning has demonstrated its versatility by addressing a diverse set of problems but also its scalability to large data sets owing to the availability of sophisticated software frameworks (such as TensorFlow and PyTorch) and efficient graphics hardware.

Computational imaging

AI can make a large contribution to clinical applications, such as diagnosis or therapy[38], but the AI algorithms involved are often dedicated to solving specific tasks that are important components in clinical workflows. For example, deciding whether to implant a cardioverter–defibrillator relies particularly on the measurement of left ventricular ejection fraction from medical images. This measurement of the ejection fraction is time consuming (around 15 min for MRI) and is subject to important variation owing to differences in imaging modality and operator expertise. An AI algorithm delineating the left ventricular endocardium in end-systolic and end-diastolic images can output the ejection fraction in a fast (a few seconds) and reproducible way[39]. This delineation is an example of an AI-based computational imaging task (FIG. 3), one of five categories of task that have been widely studied in the AI community: acquisition and reconstruction, quality control, detection, segmentation, and shape and motion analysis. Next, we review the main developments around these five computational imaging tasks.

Acquisition and reconstruction. AI for image acquisition and reconstruction tasks consists of improving the quality and reducing the time of acquisition of medical images for various modalities. In MRI[9], AI algorithms

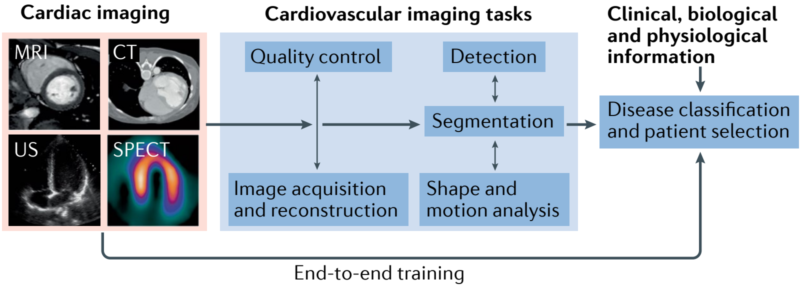

Fig. 3 | **AI-based computational imaging and AI-supported decision-making algorithms.** Several artificial intelligence (AI) algorithms for specific imaging tasks, such as image segmentation, can be applied directly to the cardiac images. AI algorithms for disease classification and patient selection tasks often require both image-derived features and clinical, biological and physiological data as the input. These algorithms can also be applied directly to the input cardiac image (the end-to-end approach). SPECT, single-photon emission CT; US, ultrasonography.

have been proposed for the detection[40] and attenuation[41] of motion artefacts caused by cardiac and respiratory motions. Other applications include the acceleration of image reconstruction[42–45] and the generation of quantitative tissue characterization images through MRI fingerprinting[46]. Similar approaches have been proposed for cardiac CT to improve reconstruction[47], image quality[48] and to remove motion artefacts[49] from coronary CT angiography with a low dose of radiation.

Quality control. Following image acquisition, the quality control task checks that all the acquired images fit a prescribed imaging standard for further processing or analysis. This task is of major interest in tackling the processing of large databases of images such as in the UK Biobank initiative. In MRI, investigators have proposed the automatic detection of possible missing basal and apical slices[50], the location of the ascending or descending aorta[51], or the presence of potential interslice motion artefacts and complete heart coverage[52,53]. In echocardiographic images from fetuses, the monitoring of several image quality criteria, including zoom, gain and organ coverage, has been proposed[54]. Quality control also applies to the delineation of cardiac structures in either a supervised[55,56] or an unsupervised[57] manner.

Detection. The detection task in this context defines a region around an anatomical structure of interest in cardiac images rather than the detection of a pathology. This task was performed in MRI to locate the myocardium[56,58,59] and the aorta[51] and for the real-time localization of catheters[60], in echocardiography for the identification of local cardiac structures[61], and in CT for the detection of 3D landmarks of vessel bifurcations[62,63].

Segmentation. Structure detection is often a prerequisite for the image segmentation task, which delineates various anatomical or pathological regions in images based on their appearance and shape. This task is time consuming when performed manually by a human expert, currently weighing heavily on the medical resources of clinical MRI departments. As for other AI imaging problems, supervised deep learning has been widely applied to address segmentation tasks[64], with much success despite the limited number of annotated cases often available in public databases. Indeed, proprietary annotations and data sets are most often used. In MRI, the segmentation of the myocardium (for example, the right ventricle and left ventricle) has attracted much attention[58,59,65–71], with a level of performance that is generally consistent with the inter-expert variation[20,39].

Despite this successful and continuously improving achievement, some remaining difficulties need to be addressed to properly handle the thin walls of the right ventricle and the extreme basal and apical slices. Enforcing some level of geometric and shape constraints for the left ventricular reconstruction through statistical atlases is often necessary to make the segmentation more robust in the presence of weak visible boundaries[66–68,72,73]. Whole-heart (ventricles, atria, aorta and pulmonary artery) image segmentation has also been achieved on both CT and MRI modalities, with satisfactory results for the four chambers[74]. Segmentation algorithms for cardiac structures in echocardiography have also been proposed[61,75–78], with levels of performance that are consistent with inter-expert variation[77]. Segmentation algorithms for the delineation of the mitral annulus in echocardiographic images has also been developed[79], as have algorithms for the segmentation of the coronary arteries in CT[11,80,81] and radiographic[82] images.

Shape and motion analysis. For a proper characterization of cardiac diseases, the use of simple indices of cardiac output such as ejection fraction is often too limited. The shape and motion analysis task aims to provide subtler measurements of cardiac motion to extract spatiotemporal patterns specific to a disease. Often, the first stage is to track the cardiac motion from time series of cardiac CT, MRI or ultrasonography images, which was the subject of a survey published in 2019 (REF.[83]). In the past 5 years, supervised and unsupervised machine learning-based image registration and tracking algorithms have been proposed as an alternative to traditional optimization-based approaches[84–89]. From the estimated displacement fields between images of the cardiac cycle, manually selected (for example, radial or longitudinal strains)[85,90,91] or learned motion features are extracted to detect abnormal motion[92], to predict survival[22] or to characterize cardiac diseases[20,65,85] such as myocardial infarction[21], pericarditis[93], heart failure with preserved ejection fraction[94] or cardiac dyssynchrony[91].

Disease classification. The output of cardiac image segmentation or motion tracking estimation tasks can produce features that, in turn, can be used to estimate anatomical and functional biomarkers as well as to perform diagnoses, disease stratification and therapy selection. Furthermore, this disease classification task can use additional features that might not derive from cardiac imaging such as clinical records (information on demographics and comorbidities)[28], biological parameters (such as omics data)[95] and physiological measurements (such as blood pressure and the electrocardiogram). Typical applications of biomarker extraction include the estimation of fractional flow reserve[96]

MRI fingerprinting
Acquisition of quantitative information from MRI scans that enables clinical decision-making on the basis of digital data rather than visual impressions.

Multi-scale
Involving several spatial or temporal resolutions of observation.

Multi-physics
Involving several different physical phenomena (such as electrophysiology and solid or fluid mechanics).

Digital twin
Patient-specific computational model (of the heart) to visualize and simulate anatomy and physiology.

Causal
In which one event (cause) contributes to the occurrence of another event (effect).

Deterministic
A system in which a given input always produces the same output (as opposed to probabilistic systems).

Mechanistic
Providing explicit information about the underlying biological or physical processes.

and coronary artery calcium scoring[97] from CT images. Classification algorithms were also developed from echocardiography for patient selection for cardiac resynchronization therapy[28,98], from late gadolinium enhancement MRI for the assessment of ventricular tachycardia[99] and from CT angiography for the prediction of successful reperfusion after an endovascular intervention[100]. Interestingly, unsupervised clustering revealed potential correlations between specific myocardial shape patterns and cardiovascular risk factors[72] and between shape features and cardiac function in the context of congenital heart diseases[24,101]. Novel approaches to diagnosis and therapy selection are aiming to perform end-to-end predictions from raw imaging signals without performing the image reconstruction task[32] (FIG. 3).

Biophysics-based AI

While AI algorithms aim to solve clinical problems from the statistical associations of features stored in images or clinical data sets, they ignore the established knowledge of human anatomy and physiology accumulated from centuries of research. Therefore, a common criticism of data-driven AI tools is that they tend to be more accurate than robust with, in some instances, the possibility of generating absurd results from unseen data. Therefore, the integration of some pre-existing anatomical and physiological knowledge into AI algorithms is important.

In parallel to the development of AI, multi-scale and multi-physics biophysical modelling of the human body has progressed tremendously[102,103], with cardiac modelling being at the forefront of this effort[104–107]. Biophysical modelling aims to simulate living organisms based on the laws of physics and on experimental knowledge of anatomy and physiology. Over the past 20 years, research has moved from the simulation of generic cardiac models to patient-specific models of the heart[107–109], creating a digital twin of a patient's heart[110]. These personalized computational models[111,112] can be used to better understand measurements in colour Doppler echocardiography[113]

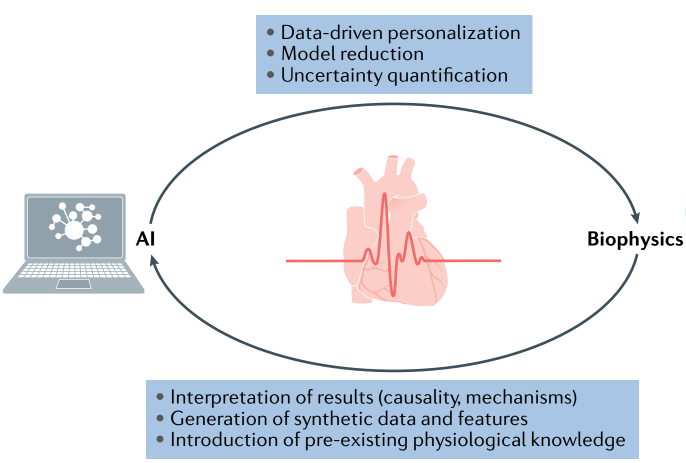

Fig. 4 | **Complementarity between AI methods and biophysical modelling.** Artificial intelligence (AI) is very efficient for statistical analysis, parameter estimation and probabilistic approaches. Biophysics can help to interpret statistical relationships discovered with the use of AI, to generate data and to integrate pre-existing medical knowledge.

and to simulate therapy in congenital heart diseases[114]. Limited proof-of-concept studies have demonstrated their predictive power for patient selection for cardiac resynchronization therapy[115] and arrhythmias[116], leading companies to develop computational tools[117–120]. However, the selection of appropriate model equations, dimensionality and parameterization for the clinical task remains crucial and highly complex[121]. The process requires close collaboration between computer scientists and clinicians to tailor models to the specific requirements of each clinical issue while preserving compatibility with a clinical workflow.

These biophysical models are by essence causal, deterministic, and mechanistic and therefore provide more explanations of the observed cardiac condition than purely data-driven AI models that are based simply on statistical associations between input and output data. This combined development of AI and biophysical models is a very promising avenue because of the central role of cardiac physiology in the interpretation of cardiovascular imaging. Therefore, efforts have been made to exploit the respective strengths of biophysical modelling and machine learning to leverage the complementary nature of model-based and data-driven AI methods[32,122–124]. Next, we summarize several ways in which AI algorithms and biophysical models can be combined (FIG. 4).

First, biophysical models can be used to generate automatically labelled synthetic data sets, which is useful because the creation of annotated data sets for supervised machine learning is often costly. This approach is useful to increase the amount of training data and is particularly relevant for rarely observed diseases and image patterns. For example, the simulation of cardiac motion in biophysical models allows the generation of large databases of labelled synthetic cardiac images for training or validating AI algorithms[125,126]. When transfer learning is performed, the training set is composed entirely of synthetic images generated by computational cardiac models to avoid the laborious annotation of real images. This approach was applied to localize ultrasound transducers in fluoroscopy images[127].

Conversely, AI algorithms can learn biophysical model equations. For example, physics-informed neural networks try to reconcile biophysical modelling with data-driven AI by constraining the output of deep learning networks to respect the laws of physics. This approach was applied in the prediction of arterial blood pressure from 4D-flow MRI[128] or cardiac electrophysiology[129]. The combination of AI tools and biophysics can also improve the estimation of biomarkers such as the fractional flow reserve[81,130], strain for echocardiography[131] or quantification for pulmonary hypertension[132].

Additionally, AI algorithms provide data-driven methods to personalize biophysical models. Indeed, often only a limited number of patient-specific biophysical parameters can be recovered from sparse and noisy image or signal content and pre-existing physiological knowledge is necessary to make relevant estimations. Supervised machine learning methods can evaluate a direct relationship between the input medical images and signals and important output biophysical

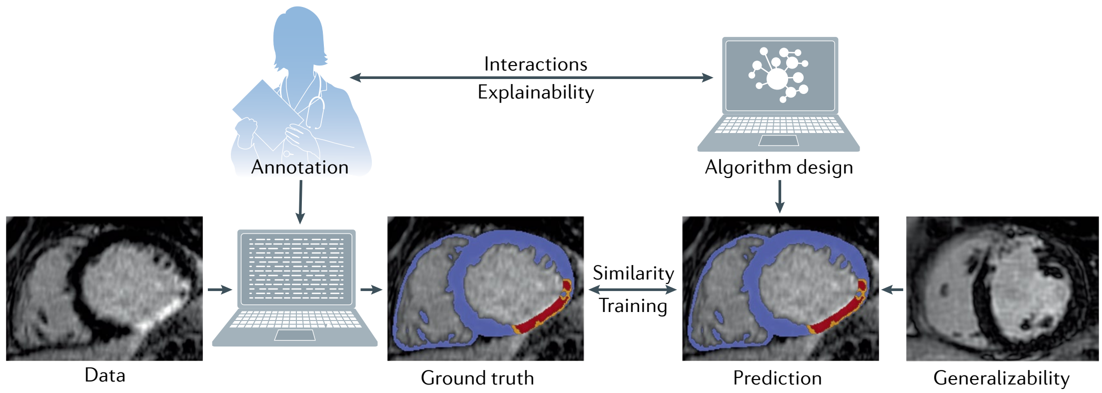

Fig. 5 | **Major challenges to the application of AI to cardiovascular imaging.** Challenges include generating ground truth, measuring the similarity between the prediction and the ground truth, generalizability, explainability and human–computer interactions. Difficulties can arise in data gathering, expert annotation, algorithm design, clinical interactions and robustness to biases in the input data. AI, artificial intelligence.

parameters. This approach was demonstrated in the field of cardiac electrophysiology to create activation maps of the heart from non-invasive imaging of cardiac electrical activity[15,16] or to predict electrophysiology patterns under stimulations from cardiac resynchronization therapy[133]. These approaches have huge potential to transform the care of patients with cardiac electrical diseases, alleviating the need for invasive catheter-based assessment of cardiac electrophysiology. This development would position imaging as the cornerstone of predictive medicine to select patients to undergo preventive or curative therapy and enabling fully non-invasive approaches to cardiac ablation in patients with arrhythmias.

Finally, simulations of cardiac functions are computationally very demanding, which is often an issue for clinical applications. AI techniques are helpful to speed up the computation of biophysical models, either through the production of simplified surrogate models or the adoption of fast numerical integration methods[134]. AI techniques can also facilitate uncertainty quantification[135], which is important because a sensitivity analysis of the recovered parameters is essential for the creation of a trustworthy digital twin of a patient's heart.

Remaining AI challenges

AI research in cardiovascular imaging analysis is progressing at a fast pace fuelled by the successes of deep learning methods but, despite an increasing number of FDA approvals for AI-based algorithms in medicine[136], its translation into effective clinical solutions remains limited. In the past 5 years, several AI-based clinical systems have emerged, for example, in patient positioning for CT acquisition[137], virtual fractional flow reserve estimation[138,139], cardiac ventricular image segmentation[140] and ultrasonography image analysis[78,79].

AI might also enable the emergence of new imaging modalities. Photon-counting CT might very well be the next revolution in medical imaging, and initial cardiac applications have shown spectacular results in terms of resolution and tissue characterization capabilities[141]. However, implementation in clinical practice will require the reconstruction (and segmentation) of whole-heart data sets with near 100 μm^3 resolution. Achieving this level of detail in, for example, 40 patients attending a daily clinic will not be practically achievable without the use of AI. In this context, AI can be seen not only as a tool to improve an already existing imaging technology but as a mandatory step for a new imaging technology to reach clinical practice.

However, a gap still exists between the number of computational tools developed in academic research and the number of tools available in clinical practice. This gap is partially caused by the stringent regulatory framework for designing and distributing these novel clinical solutions but also due to a number of challenges in medical image analysis[142] and in AI approaches that need to be overcome to widen AI applicability in clinical practice. Next, we discuss four of these challenges (FIG. 5; BOX 1).

AI algorithm design. A first set of challenges is related to the design of AI algorithms. First, the learning process is based on the computational optimization of a cost function that measures the similarity between the output produced by the algorithm and the ground truth. For example, to delineate a structure such as the left ventricle in a cardiac image, an AI algorithm typically tries to maximize the overlap between the left ventricle delineation provided by the algorithm and the ground truth provided by an expert. Selecting a cost function influences the performance in terms of accuracy (how the output differs from the ground truth) and robustness (how consistent are the outputs from a large data set). Often, accuracy is overvalued in academic research, whereas robustness is mandatory for clinical adoption. Second, finding the best architecture of neural networks to efficiently solve a given task remains a difficult problem, although automated machine learning is making promising advances to automatically provide problem-specific neural networks to non-expert AI users[143]. Third, there are technological barriers to the deployment of deep learning methods such as the limited memory of graphics processing units for handling large volumetric images, the large amount of electrical energy required during training and the difficulty of running them on hand-held computing devices.

Uncertainty quantification
Determination of how the output of an algorithm varies if some of its parameters or input are not exactly known.

Box 1 | **AI challenges in cardiovascular imaging**

- Algorithm design
  - Cost function
  - Evaluation
  - Computational cost
- Training data
  - Expert labelling
  - Database size
- Generalization performance
  - Representativeness and bias
  - Transfer learning
- Clinical use
  - Explainability
  - Security and privacy
  - Trust

AI, artificial intelligence.

Appropriate training data. A second set of challenges specific to machine learning algorithms is their need for appropriate training data. In many cases, supervised learning is used to solve a given task, thereby requiring the annotation of cardiovascular images. However, creating annotations (such as delineations of anatomical structures, image labels and landmarks) is time consuming and expensive for experts and requires efficient, often cloud-based platforms to streamline the process. Therefore, the production of high-quality annotations is often prohibitive for large databases of images. Furthermore, for some imaging problems, such as cardiac motion tracking, clinicians cannot provide detailed information (such as the correspondence of landmarks over the cardiac cycle) but only qualitative assessments (such as the presence of a septal flash motion).

Several alternatives have been proposed to tackle the issue of labelling medical images. For example, crowdsourcing platforms, whereby annotations are produced by many minimally trained individuals instead of a small number of highly trained experts, might be used to scale up the availability of annotations[144]. Additionally, active learning algorithms aim to limit the need for annotations from a human expert only to the cases in which those annotations would most benefit the learning process[145]. These algorithms allow the seamless integration of the online training of an AI algorithm with the creation of annotations. Given that the AI algorithm continuously improves its performance, experts have to annotate increasingly challenging images, thereby avoiding the need to consider images that are already well covered by the AI algorithm.

Another approach to leverage image annotation is to automatically create synthetic but realistic images with their labels from a mathematical model. For example, as discussed above, biophysical models of the heart were used to generate cardiac image sequences corresponding to various simulated physiological conditions (such as the presence of ischaemic or infarcted regions or left bundle branch block)[125,126]. This approach requires transfer learning, which is a methodology to apply an algorithm to a data set that has some differences from the training data set.

Finally, semi-supervised approaches leverage a large amount of unlabelled data by optimizing some additional specific criteria[85] or by solving self-supervision tasks[146]. Semi-supervised approaches can be suitable when, for example, combining cardiovascular imaging with omics data.

Generalization. A third set of challenges is related to the difficulty of generalizing the performance of AI methods to images or cases unseen in the training data set. The issue of generalizability is especially relevant to deep learning methods that are parameterized by a large number of coefficients and, therefore, need many training examples to optimize them. A related challenge is making correct predictions from data sets that slightly vary from the original training set, for example, images acquired with different scanner characteristics (such as 1.5 T versus 3.0 T MRI images), different scanner vendors or from a different patient population. Another associated risk is the production of decision-support systems that reproduce or even exacerbate some biases that were present in the training data set, in particular linked to equipment, sex, ethnicity or pathology-driven specificities. This risk is especially important for the processing of rare pathology cases such as in congenital heart diseases[147]. The creation of multicentre imaging data sets based on multiple vendor acquisition devices is required to decrease biases in the training data set. Methodological approaches can also be used to limit the risk of data overfitting by learning a high-level representation of the image content[148] or by solving additional tasks to enforce semantic information in the neural networks[146].

Another strategy is to perform transfer learning, in which AI algorithms are trained on source domains where annotations are widely available[127]. Despite the recognized difficulty of AI to cope with unseen images, the problem of generalizability existed before the application of AI to the field of cardiac imaging. Indeed, despite common decision-making flow diagrams issued by medical societies, patient management has long been highly dependent on the performance of the imaging systems and experts available locally. This limitation is inherent to the medical imaging field which, in contrast to biological testing, is not designed to develop industry-wide standards but is instead prone to generating highly variable data, with each vendor aiming to produce a product with improved image contrast and/or resolution. This rapid pace of innovation is a strength of the field but also comes with a generalization challenge and, in that context, AI might be viewed more as a solution than as part of the problem. Indeed, particularly for imaging markers applied for primary prevention, which are designed to address an issue at the population scale, AI has the potential to build robust standards from highly heterogeneous data sources. The left ventricular ejection fraction is a striking example because it is a weak predictor on which all modalities had to compromise for the sake of standardization, thereby leaving aside the much richer information that is obtainable by tissue characterization techniques. These challenges call for a thorough and standardized way of evaluating this new approach. Efforts are being made to propose an evaluation methodology[149]. This methodology

Explainability
An explainable algorithm must produce details that make its process easy to understand.

will have to involve prospective studies to be fully convincing, which is linked to the next set of challenges.

Translation to clinical workflow. A fourth set of challenges is linked to the insertion of AI methods into the clinical workflow. First, these methods need to be trusted by clinicians, which might be hampered by the lack of explainability of many AI algorithms. Any explainable algorithm should produce details or reasons to make its process clear or easy to understand[150]. Explainability is not only important for the wide adoption of AI technologies by medical staff but is also required to some extent by legal data-protection frameworks such as the European General Data Protection Regulation. Data-driven AI approaches such as deep learning are considered 'black-box' methods and the development of 'explainable AI' is an active field of research. One possible solution is to harness the power of deep learning to efficiently extract interpretable features for disease classification[85]. Another avenue is to provide visible explanations of the output of neural networks after their application to medical images[150].

Second, the adoption of AI methods as decision support systems for important clinical problems might create an excessive confidence in these tools among physicians due to their high accuracy in most common cases. This confidence might lead to a deskilling phenomenon of these professionals, who consequently might not detect potential failures of the AI systems[151]. This issue can be addressed by the estimation of confidence scores in decision support systems, with a threshold below which the input of clinicians becomes mandatory. More generally, the issue calls for the development of dedicated clinical interfaces and workflows that preserve the expertise of the user. All these efforts to create trustworthy AI algorithms will encourage a wider use of AI tools in clinical practice[152]. Several active multidisciplinary efforts are under way to achieve this aim[153]. Important questions about ethics, in particular about the use of personal data in AI applications, must also be addressed. Finally, important regulatory issues concerning security, privacy and liability must be clarified.

Conclusions

Cardiovascular imaging has several distinctive characteristics that can be viewed as both challenges and opportunities for AI: it combines structural and functional information about a patient's physiology; it is redundant, agile and ever-changing given the wide variety of modalities and techniques to assess the heart and the very rapid developments in image acquisition and reconstruction; it is computationally demanding given the multiple scales on which the organ can be analysed; and it directly affects patient management given the broad spectrum of cardiac interventions developed over the past two decades, all of which require images for patient selection, preoperative planning or even direct intraprocedural guidance.

Over the past decade, multiple proof-of-concept studies have outlined the extraordinary potential of AI to transform the way that cardiac images are prescribed, acquired, reconstructed, analysed and used to tailor patient care. In daily clinical practice, AI is currently mostly used to automate segmentation. The implementation of AI in predictive medicine is a far more attractive prospect but will certainly require more time and validation efforts, particularly to ensure generalizability. Large-scale collaborations are needed to provide high-quality multicentre and multimodality data sets.

The interactions between AI and pre-existing knowledge of anatomy, physiology, biophysics and experts opens up many possibilities. The opportunities of integrating this knowledge into digital twins of patients' hearts are fascinating. These approaches will introduce clinicians and patients to personalized medicine, providing a powerful aid to medical decision-making, therapy selection and target identification. Finally, the addition of in silico simulations to digital twins of patients' hearts will introduce a new era of medical training and pharmacological or non-pharmacological therapy testing, with the prediction of outcomes or adverse effects.

AI could be the tool we have been waiting for to put imaging at the cornerstone of patient management in cardiology, ensuring that any piece of information present in cardiac images is effectively used to improve the diagnosis, prediction and treatment of cardiac diseases. We are not there yet and, for this objective to be achieved, AI will have to meet the highest standards and, perhaps even more importantly, gain the trust of both patients and clinicians.

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1. Greenspan, H., van Ginneken, B. & Summers, R. M. Guest editorial deep learning in medical imaging: overview and future promise of an exciting new technique. *IEEE Trans. Med. Imaging* **35**, 1153–1159 (2016).
2. LeCun, Y., Bengio, Y. & Hinton, G. Deep learning. *Nature* **521**, 436–444 (2015).
3. Dey, D. et al. Artificial intelligence in cardiovascular imaging. *J. Am. Coll. Cardiol.* **73**, 1317–1335 (2019).
4. Siegersma, K. R. et al. Artificial intelligence in cardiovascular imaging: state of the art and implications for the imaging cardiologist. *Neth. Heart J.* **27**, 403–413 (2019).
5. Henglin, M. et al. Machine learning approaches in cardiovascular imaging. *Circ. Cardiovasc. Imaging* **10**, e005614 (2017).
6. O'Regan, D. P. Putting machine learning into motion: applications in cardiovascular imaging. *Clin. Radiol.* **75**, 33–37 (2019).
7. Seetharam, K., Shrestha, S. & Sengupta, P. P. Artificial intelligence in cardiovascular medicine. *Curr. Treat. Options Cardiovasc. Med.* **21**, 25 (2019).
8. Litjens, G. et al. State-of-the-art deep learning in cardiovascular image analysis. *JACC Cardiovasc. Imaging* **12**, 1549–1565 (2019).
9. Leiner, T. et al. Machine learning in cardiovascular magnetic resonance: basic concepts and applications. *J. Cardiovasc. Magn. Reson.* **21**, 61 (2019).
10. Lundervold, A. S. & Lundervold, A. An overview of deep learning in medical imaging focusing on MRI. *Z. Med. Phys.* **29**, 102–127 (2019).
11. Hampe, N., Wolterink, J. M., van Velzen, S. G. M., Leiner, T. & Išgum, I. Machine learning for assessment of coronary artery disease in cardiac CT: a survey. *Front. Cardiovasc. Med.* **6**, 172 (2019).
12. Alsharqi, M. et al. Artificial intelligence and echocardiography. *Echo Res. Pract.* **5**, R115–R125 (2018).
13. van Sloun, R. J. G., Cohen, R. & Eldar, Y. C. Deep learning in ultrasound imaging. *Proc. IEEE* **108**, 11–29 (2020).
14. Cluitmans, M. et al. Validation and opportunities of electrocardiographic imaging: from technical achievements to clinical applications. *Front. Physiol.* **9**, 1305 (2018).
15. Alawad, M. & Wang, L. Learning domain shift in simulated and clinical data: localizing the origin of ventricular activation from 12-lead electrocardiograms. *IEEE Trans. Med. Imaging* **38**, 1172–1184 (2019).
16. Bacoyannis, T., Krebs, J., Cedilnik, N., Cochet, H. & Sermesant, M. in *Functional Imaging and Modeling of the Heart* Ch. 3 (eds Coudière, Y., Ozenne, V., Vigmond, E. & Zemzemi, N.) 20–28 (Springer, 2019).
17. Bai, W. et al. A population-based phenome-wide association study of cardiac and aortic structure and function. *Nat. Med.* **26**, 1654–1662 (2020).
18. Petersen, S. E., Abdulkareem, M. & Leiner, T. Artificial intelligence will transform cardiac imaging — opportunities and challenges. *Front. Cardiovasc. Med.* **6**, 169 (2019).
19. Attia, Z. I. et al. Screening for cardiac contractile dysfunction using an artificial intelligence-enabled electrocardiogram. *Nat. Med.* **25**, 70–74 (2019).

20. Bernard, O. et al. Deep learning techniques for automatic MRI cardiac multi-structures segmentation and diagnosis: is the problem solved? *IEEE Trans. Med. Imaging* **37**, 2514–2525 (2018).
21. Zhang, N. et al. Deep learning for diagnosis of chronic myocardial infarction on nonenhanced cardiac cine MRI. *Radiology* **291**, 606–617 (2019).
22. Bello, G. A. et al. Deep learning cardiac motion analysis for human survival prediction. *Nat. Mach. Intell.* **1**, 95–104 (2019).
23. Bruse, J. L. et al. in *Statistical Atlases and Computational Models of the Heart. Imaging and Modelling Challenges* Ch. 3 (eds Camara, O. et al.) 21–29 (Springer, 2016).
24. Leonardi, B. et al. Computational modelling of the right ventricle in repaired tetralogy of Fallot: can it provide insight into patient treatment? *Eur. Heart J. Cardiovasc. Imaging* **14**, 381–386 (2013).
25. Grbic, S. et al. Personalized mitral valve closure computation and uncertainty analysis from 3D echocardiography. *Med. Image Anal.* **35**, 238–249 (2017).
26. European Society of Radiology. What the radiologist should know about artificial intelligence — an ESR white paper. *Insights Imaging* **10**, 44 (2019).
27. James, G., Witten, D., Hastie, T. & Tibshirani, R. in *An Introduction to Statistical Learning* Ch. 2 26–28 (Springer, 2013).
28. Hu, S.-Y. et al. Can machine learning improve patient selection for cardiac resynchronization therapy? *PLoS ONE* **14**, e0222397 (2019).
29. Hosny, A., Parmar, C., Quackenbush, J., Schwartz, L. H. & Aerts, H. J. W. L. Artificial intelligence in radiology. *Nat. Rev. Cancer* **18**, 500–510 (2018).
30. Cheplygina, V., de Bruijne, M. & Pluim, J. P. W. Not-so-supervised: a survey of semi-supervised, multi-instance, and transfer learning in medical image analysis. *Med. Image Anal.* **54**, 280–296 (2019).
31. Mlynarski, P., Delingette, H., Criminisi, A. & Ayache, N. Deep learning with mixed supervision for brain tumor segmentation. *J. Med. Imaging* **6**, 034002 (2019).
32. Rueckert, D. & Schnabel, J. A. Model-based and data-driven strategies in medical image computing. *Proc. IEEE* **108**, 110–124 (2020).
33. Saba, L. et al. The present and future of deep learning in radiology. *Eur. J. Radiol.* **114**, 14–24 (2019).
34. Litjens, G. et al. A survey on deep learning in medical image analysis. *Med. Image Anal.* **42**, 60–88 (2017).
35. Ronneberger, O., Fischer, P. & Brox, T. in *Medical Image Computing and Computer-Assisted Intervention — MICCAI 2015* (eds Navab, N., Hornegger, J., Wells, W. M. & Frangi, A. F.) 234–241 (Springer, 2015).
36. Goodfellow, I. et al. in *Advances in Neural Information Processing Systems 27* (eds Ghahramani, Z., Welling, M., Cortes, C., Lawrence, N. D. & Weinberger, K. Q.) 2672–2680 (Curran Associates, 2014).
37. Kingma, D. P. & Welling, M. An introduction to variational autoencoders. *Found. Trends Mach. Learn.* **12**, 307–392 (2019).
38. Pesapane, F., Codari, M. & Sardanelli, F. Artificial intelligence in medical imaging: threat or opportunity? Radiologists again at the forefront of innovation in medicine. *Eur. Radiol. Exp.* **2**, 35 (2018).
39. Bhuva, A. et al. A multicenter, scan-rescan, human and machine learning CMR study to test generalizability and precision in imaging biomarker analysis. *Circ. Cardiovasc. Imaging* **12**, e009214 (2019).
40. Oksuz, I. et al. Automatic CNN-based detection of cardiac MR motion artefacts using k-space data augmentation and curriculum learning. *Med. Image Anal.* **55**, 136–147 (2019).
41. Oksuz, I. et al. in *Medical Image Computing and Computer Assisted Intervention — MICCAI 2019* (eds Shen, D. et al.) 695–703 (Springer, 2019).
42. Schlemper, J. et al. in *Medical Image Computing and Computer Assisted Intervention — MICCAI 2019* (eds Shen, D. et al.) 57–64 (Springer, 2019).
43. Hyun, C. M., Kim, H. P., Lee, S. M., Lee, S. & Seo, J. K. Deep learning for undersampled MRI reconstruction. *Phys. Med. Biol.* **63**, 135007 (2018).
44. Qin, C. et al. Convolutional recurrent neural networks for dynamic MR image reconstruction. *IEEE Trans. Med. Imaging* **38**, 280–290 (2019).
45. Bustin, A., Fuin, N., Botnar, R. M. & Prieto, C. From compressed-sensing to artificial intelligence-based cardiac MRI reconstruction. *Front. Cardiovasc. Med.* **7**, 17 (2020).
46. Oksuz, I. et al. Magnetic resonance fingerprinting using recurrent neural networks. *IEEE Int. Symp. Biomed. Imaging* https://doi.org/10.1109/ISBI.2019.8759502 (2019).
47. Willemink, M. J. & Noël, P. B. The evolution of image reconstruction for CT-from filtered back projection to artificial intelligence. *Eur. Radiol.* **29**, 2185–2195 (2019).
48. Green, M., Marom, E. M., Konen, E., Kiryati, N. & Mayer, A. 3-D Neural denoising for low-dose Coronary CT Angiography (CCTA). *Comput. Med. Imaging Graph.* **70**, 185–191 (2018).
49. Lossau, T. et al. Motion artifact recognition and quantification in coronary CT angiography using convolutional neural networks. *Med. Image Anal.* **52**, 68–79 (2019).
50. Zhang, L. et al. in *Simulation and Synthesis in Medical Imaging* (eds Tsaftaris, S. A., Gooya, A., Frangi, A. F. & Prince, J. L.) 138–145 (Springer, 2016).
51. Biasiolli, L. et al. Automated localization and quality control of the aorta in cine CMR can significantly accelerate processing of the UK Biobank population data. *PLoS ONE* **14**, e0212272 (2019).
52. Tarroni, G. et al. Learning-based quality control for cardiac MR images. *IEEE Trans. Med. Imaging* **38**, 1127–1138 (2019).
53. Zhang, L. et al. Automatic assessment of full left ventricular coverage in cardiac cine magnetic resonance imaging with fisher discriminative 3D CNN. *IEEE Trans. Biomed. Eng.* **66**, 1975–1986 (2018).
54. Dong, J. et al. A generic quality control framework for fetal ultrasound cardiac four-chamber planes. *IEEE J. Biomed. Health Inform.* **24**, 931–942 (2019).
55. Robinson, R. et al. Automated quality control in image segmentation: application to the UK Biobank cardiovascular magnetic resonance imaging study. *J. Cardiovasc. Magn. Reson.* **21**, 18 (2019).
56. Albà, X. et al. Automatic initialization and quality control of large-scale cardiac MRI segmentations. *Med. Image Anal.* **43**, 129–141 (2018).
57. Audelan, B. & Delingette, H. in *Medical Image Computing and Computer Assisted Intervention — MICCAI 2019* (eds Shen, D. et al.) 21–29 (Springer, 2019).
58. Vigneault, D. M., Xie, W., Ho, C. Y., Bluemke, D. A. & Noble, J. A. Ω-Net (Omega-Net): Fully automatic, multi-view cardiac MR detection, orientation, and segmentation with deep neural networks. *Med. Image Anal.* **48**, 95–106 (2018).
59. Zheng, Q., Delingette, H., Duchateau, N. & Ayache, N. 3-D consistent and robust segmentation of cardiac images by deep learning with spatial propagation. *IEEE Trans. Med. Imaging* **37**, 2137–2148 (2018).
60. Ambrosini, P. et al. in *Medical Image Computing and Computer-Assisted Intervention — MICCAI 2017* (eds Descoteaux, M. et al) 577–585 (Springer, 2017).
61. Ghorbani, A. et al. Deep learning interpretation of echocardiograms. *NPJ Digital Med.* **3**, 10 (2020).
62. Ghesu, F.-C. et al. Multi-scale deep reinforcement learning for real-time 3D-landmark detection in CT scans. *IEEE Trans. Pattern Anal. Mach. Intell.* **41**, 176–189 (2019).
63. Noothout, J. M. H. et al. Deep learning-based regression and classification for automatic landmark localization in medical images. *IEEE Trans. Med. Imaging* **39**, 4011–4022 (2020).
64. Chen, C. et al. Deep learning for cardiac image segmentation: a review. *Front. Cardiovasc. Med.* **7**, 25 (2020).
65. Isensee, F. et al. in *Statistical Atlases and Computational Models of the Heart. ACDC and MMWHS Challenges* (eds Pop, M. et al.) 120–129 (Springer, 2018).
66. Clough, J. R., Oksuz, I., Byrne, N., Schnabel, J. A. & King, A. P. in *Information Processing in Medical Imaging* (eds Chung, A. C. S., Gee, J. C., Yushkevich, P. A. & Bao, S.) 16–28 (Springer, 2019).
67. Duan, J. et al. Automatic 3D Bi-ventricular segmentation of cardiac images by a shape-refined multi- task deep learning approach. *IEEE Trans. Med. Imaging* **38**, 2151–2164 (2019).
68. Albà, X. et al. An algorithm for the segmentation of highly abnormal hearts using a generic statistical shape model. *IEEE Trans. Med. Imaging* **35**, 845–859 (2016).
69. Liao, F., Chen, X., Hu, X. & Song, S. Estimation of the volume of the left ventricle from MRI images using deep neural networks. *IEEE Trans. Cybern.* **49**, 495–504 (2019).
70. Margeta, J. et al. in *Statistical Atlases and Computational Models of the Heart. Imaging and Modelling Challenges* (eds Camara, O. et al.) 49–56 (Springer, 2014).
71. Bai, W. et al. Automated cardiovascular magnetic resonance image analysis with fully convolutional networks. *J. Cardiovasc. Magn. Reson.* **20**, 65 (2018).
72. Gilbert, K. et al. Independent left ventricular morphometric atlases show consistent relationships with cardiovascular risk factors: A UK biobank study. *Sci. Rep.* **9**, 1130 (2019).
73. Lee, M. C. H., Petersen, K., Pawlowski, N., Glocker, B. & Schaap, M. Tetris: template transformer networks for image segmentation with shape priors. *IEEE Trans. Med. Imaging* **38**, 2596–2606 (2019).
74. Zhuang, X. et al. Evaluation of algorithms for multi-modality whole heart segmentation: an open-access grand challenge. *Med. Image Anal.* **58**, 101537 (2019).
75. Gilbert, A. et al. in *Smart Ultrasound Imaging and Perinatal, Preterm and Paediatric Image Analysis* (eds Wang, Q. et al.) 29–37 (Springer, 2019).
76. Huang, X. et al. Contour tracking in echocardiographic sequences via sparse representation and dictionary learning. *Med. Image Anal.* **18**, 253–271 (2014).
77. Leclerc, S. et al. Deep learning for segmentation using an open large-scale dataset in 2D echocardiography. *IEEE Trans. Med. Imaging* **38**, 2198–2210 (2019).
78. Asch, F. M. et al. Automated echocardiographic quantification of left ventricular ejection fraction without volume measurements using a machine learning algorithm mimicking a human expert. *Circ. Cardiovasc. Imaging* **12**, e009303 (2019).
79. Andreassen, B. S., Veronesi, F., Gerard, O., Solberg, A. H. S. & Samset, E. Mitral annulus segmentation using deep learning in 3-D transesophageal echocardiography. *IEEE J. Biomed. Health Inform.* **24**, 994–1003 (2020).
80. Wolterink, J. M., Leiner, T. & Išgum, I. in *Graph Learning in Medical Imaging* (eds Zhang, D., Zhou, L., Jie, B. & Liu, M.) 62–69 (Springer, 2019).
81. Itu, L. et al. A machine-learning approach for computation of fractional flow reserve from coronary computed tomography. *J. Appl. Physiol.* **121**, 42–52 (2016).
82. Yang, S. et al. Deep learning segmentation of major vessels in X-ray coronary angiography. *Sci. Rep.* **9**, 16897 (2019).
83. Duchateau, N., King, A. P. & De Craene, M. Machine learning approaches for myocardial motion and deformation analysis. *Front. Cardiovasc. Med.* **6**, 190 (2019).
84. Krebs, J., Delingette, H., Mailhe, B., Ayache, N. & Mansi, T. Learning a probabilistic model for diffeomorphic registration. *IEEE Trans. Med. Imaging* **38**, 2165–2176 (2019).
85. Zheng, Q., Delingette, H. & Ayache, N. Explainable cardiac pathology classification on cine MRI with motion characterization by semi-supervised learning of apparent flow. *Med. Image Anal.* **56**, 80–95 (2019).
86. Yan, W., Wang, Y., van der Geest, R. J. & Tao, Q. Cine MRI analysis by deep learning of optical flow: adding the temporal dimension. *Comput. Biol. Med.* **111**, 103356 (2019).
87. Parajuli, N. et al. Flow network tracking for spatiotemporal and periodic point matching: applied to cardiac motion analysis. *Med. Image Anal.* **55**, 116–135 (2019).
88. Lu, A. et al. in *Medical Image Computing and Computer-Assisted Intervention — MICCAI 2017* (eds Descoteaux, M. et al.) 323–331 (Springer, 2017).
89. Song, S. et al. Deep motion tracking from multiview angiographic image sequences for synchronization of cardiac phases. *Phys. Med. Biol.* **64**, 025018 (2019).
90. Attar, R. et al. Quantitative CMR population imaging on 20,000 subjects of the UK Biobank imaging study: LV/RV quantification pipeline and its evaluation. *Med. Image Anal.* **56**, 26–42 (2019).
91. Mantilla, J. J. et al. Discriminative dictionary learning for local LV wall motion classification in cardiac MRI. *Expert. Syst. Appl.* **129**, 286–295 (2019).
92. Duchateau, N., De Craene, M., Piella, G. & Frangi, A. F. Constrained manifold learning for the characterization of pathological deviations from normality. *Med. Image Anal.* **16**, 1532–1549 (2012).
93. Sengupta, P. P. et al. Cognitive machine-learning algorithm for cardiac imaging: a pilot study for differentiating constrictive pericarditis from restrictive cardiomyopathy. *Circ. Cardiovasc. Imaging* **9**, e004330 (2016).

94. Sanchez-Martinez, S. et al. Characterization of myocardial motion patterns by unsupervised multiple kernel learning. *Med. Image Anal.* **35**, 70–82 (2017).
95. Meyer, H. V. et al. Genetic and functional insights into the fractal structure of the heart. *Nature* **584**, 589–594 (2020).
96. Zreik, M. et al. Deep learning analysis of coronary arteries in cardiac CT angiography for detection of patients requiring invasive coronary angiography. *IEEE Trans. Med. Imaging* **36**, 1545–1557 (2019).
97. Martin, S. S. et al. Evaluation of a deep learning-based automated CT coronary artery calcium scoring algorithm. *JACC Cardiovasc. Imaging* **13**, 524–526 (2019).
98. Cikes, M. et al. Machine learning-based phenogrouping in heart failure to identify responders to cardiac resynchronization therapy. *Eur. J. Heart Fail.* **21**, 74–85 (2019).
99. Alis, D., Guler, A., Yergin, M. & Asmakutlu, O. Assessment of ventricular tachyarrhythmia in patients with hypertrophic cardiomyopathy with machine learning-based texture analysis of late gadolinium enhancement cardiac MRI. *Diagn. Interv. Imaging* **101**, 137–146 (2019).
100. Hilbert, A. et al. Data-efficient deep learning of radiological image data for outcome prediction after endovascular treatment of patients with acute ischemic stroke. *Comput. Biol. Med.* **115**, 103516 (2019).
101. Bruse, J. L. et al. Detecting clinically meaningful shape clusters in medical image data: metrics analysis for hierarchical clustering applied to healthy and pathological aortic arches. *IEEE Trans. Biomed. Eng.* **64**, 2373–2383 (2017).
102. Hunter, P. The virtual physiological human: the physiome project aims to develop reproducible, multiscale models for clinical practice. *IEEE Pulse* **7**, 36–42 (2016).
103. Ayache, N. Medical imaging informatics: towards a personalized computational patient. *Yearb. Med. Inform.* **25** (Suppl. 1), S8–S9 (2016).
104. Bassingthwaighte, J., Hunter, P. & Noble, D. The cardiac physiome: perspectives for the future. *Exp. Physiol.* **94**, 597–605 (2009).
105. Chapelle, D., Le Tallec, P., Moireau, P. & Sorine, M. Energy-preserving muscle tissue model: formulation and compatible discretizations. *Int. J. Mult. Comp. Eng.* **10**, 189–211 (2012).
106. Suinesiaputra, A., McCulloch, A. D., Nash, M. P., Pontre, B. & Young, A. A. Cardiac image modelling: Breadth and depth in heart disease. *Med. Image Anal.* **33**, 38–43 (2016).
107. Niederer, S. A., Lumens, J. & Trayanova, N. A. Computational models in cardiology. *Nat. Rev. Cardiol.* **16**, 100–111 (2019).
108. Comaniciu, D., Engel, K., Georgescu, B. & Mansi, T. Shaping the future through innovations: from medical imaging to precision medicine. *Med. Image Anal.* **33**, 19–26 (2016).
109. Molléro, R. et al. Multifidelity-CMA: a multifidelity approach for efficient personalisation of 3D cardiac electromechanical models. *Biomech. Model. Mechanobiol.* **17**, 285–300 (2018).
110. Corral-Acero, J. et al. The 'Digital Twin' to enable the vision of precision cardiology. *Eur. Heart J.* **41**, 4556–4564 (2020).
111. Chabiniok, R. et al. Multiphysics and multiscale modelling, data-model fusion and integration of organ physiology in the clinic: ventricular cardiac mechanics. *Interface Focus.* **6**, 20150083 (2016).
112. Sermesant, M. et al. Toward patient-specific myocardial models of the heart. *Heart Fail. Clin.* **4**, 289–301 (2008).
113. This, A., Morales, H. G., Bonnefous, O., Fernández, M. A. & Gerbeau, J.-F. A pipeline for image based intracardiac CFD modeling and application to the evaluation of the PISA method. *Comput. Methods Appl. Mech. Eng.* **358**, 112627 (2020).
114. Vignon-Clementel, I. E., Marsden, A. L. & Feinstein, J. A. A primer on computational simulation in congenital heart disease for the clinician. *Prog. Pediatr. Cardiol.* **30**, 3–13 (2010).
115. Sermesant, M. et al. Patient-specific electromechanical models of the heart for the prediction of pacing acute effects in CRT: a preliminary clinical validation. *Med. Image Anal.* **16**, 201–215 (2012).
116. Chen, Z. et al. Biophysical modeling predicts ventricular tachycardia inducibility and circuit morphology: a combined clinical validation and computer modeling approach. *J. Cardiovasc. Electrophysiol.* **27**, 851–860 (2016).
117. Baillargeon, B., Rebelo, N., Fox, D. D., Taylor, R. L. & Kuhl, E. The living heart project: a robust and integrative simulator for human heart function. *Eur. J. Mech. A Solids* **48**, 38–47 (2014).
118. Kayvanpour, E. et al. Towards personalized cardiology: multi-scale modeling of the failing heart. *PLoS ONE* **10**, e0134869 (2015).
119. Zhang, F. et al. Towards patient-specific modeling of mitral valve repair: 3D transesophageal echocardiography-derived parameter estimation. *Med. Image Anal.* **35**, 599–609 (2017).
120. Lluch, È. et al. Breaking the state of the heart: meshless model for cardiac mechanics. *Biomech. Model. Mechanobiol.* **18**, 1549–1561 (2019).
121. Garny, A., Noble, D. & Kohl, P. Dimensionality in cardiac modelling. *Prog. Biophys. Mol. Biol.* **87**, 47–66 (2005).
122. Neumann, D. et al. A self-taught artificial agent for multi-physics computational model personalization. *Med. Image Anal.* **34**, 52–64 (2016).
123. Lozoya, R. C. et al. Model-based feature augmentation for cardiac ablation target learning from images. *IEEE Trans. Biomed. Eng.* **66**, 30–40 (2018).
124. Alber, M. et al. Integrating machine learning and multiscale modeling-perspectives, challenges, and opportunities in the biological, biomedical, and behavioral sciences. *NPJ Digital Med.* **2**, 115 (2019).
125. Prakosa, A. et al. Generation of synthetic but visually realistic time series of cardiac images combining a biophysical model and clinical images. *IEEE Trans. Med. Imaging* **32**, 99–109 (2013).
126. Duchateau, N., Sermesant, M., Delingette, H. & Ayache, N. Model-based generation of large databases of cardiac images: synthesis of pathological cine MR sequences from real healthy cases. *IEEE Trans. Med. Imaging* **37**, 755–766 (2018).
127. Heimann, T., Mountney, P., John, M. & Ionasec, R. Real-time ultrasound transducer localization in fluoroscopy images by transfer learning from synthetic training data. *Med. Image Anal.* **18**, 1320–1328 (2014).
128. Kissas, G. et al. Machine learning in cardiovascular flows modeling: predicting arterial blood pressure from non-invasive 4D flow MRI data using physics-informed neural networks. *Comput. Methods Appl. Mech. Eng.* **358**, 112623 (2020).
129. Ayed, I., Cedilnik, N., Gallinari, P. & Sermesant, M. in *Functional Imaging and Modeling of the Heart* (eds Coudière, Y., Ozenne, V., Vigmond, E. & Zemzemi, N.) 55–63 (Springer, 2019).
130. Coenen, A. et al. Diagnostic accuracy of a machine-learning approach to coronary computed tomographic angiography-based fractional flow reserve: result from the MACHINE consortium. *Circ. Cardiovasc. Imaging* **11**, e007217 (2018).
131. Papademetris, X., Sinusas, A. J., Dione, D. P. & Duncan, J. S. Estimation of 3D left ventricular deformation from echocardiography. *Med. Image Anal.* **5**, 17–28 (2001).
132. Finsberg, H. et al. Computational quantification of patient-specific changes in ventricular dynamics associated with pulmonary hypertension. *Am. J. Physiol. Heart Circ. Physiol.* **317**, H1363–H1375 (2019).
133. Giffard-Roisin, S. et al. Transfer learning from simulations on a reference anatomy for ECGI in personalized cardiac resynchronization therapy. *IEEE Trans. Biomed. Eng.* **66**, 343–353 (2019).
134. Meister, F. et al. Deep learning acceleration of total Lagrangian explicit dynamics for soft tissue mechanics. *Comput. Methods Appl. Mech. Eng.* **358**, 112628 (2020).
135. Konukoglu, E. et al. Efficient probabilistic model personalization integrating uncertainty on data and parameters: application to eikonal-diffusion models in cardiac electrophysiology. *Prog. Biophys. Mol. Biol.* **107**, 134–146 (2011).
136. The Medical Futurist. FDA approvals for smart algorithms in medicine in one giant infographic. *Medical Futurist* https://medicalfuturist.com/fda-approvals-for-algorithms-in-medicine (2019).
137. Saltybaeva, N., Schmidt, B., Wimmer, A., Flohr, T. & Alkadhi, H. Precise and automatic patient positioning in computed tomography: avatar modeling of the patient surface using a 3-dimensional camera. *Invest. Radiol.* **53**, 641–646 (2018).
138. Taylor, C. A., Fonte, T. A. & Min, J. K. Computational fluid dynamics applied to cardiac computed tomography for noninvasive quantification of fractional flow reserve: scientific basis. *J. Am. Coll. Cardiol.* **61**, 2233–2241 (2013).
139. Lu, M. T. et al. Noninvasive FFR derived from coronary CT angiography: management and outcomes in the PROMISE trial. *JACC Cardiovasc. Imaging* **10**, 1350–1358 (2017).
140. Bluemke, D. A. Radiology in 2018: are you working with AI or being replaced by AI? *Radiology* **287**, 365–366 (2018).
141. Willemink, M. J. et al. Photon-counting CT: technical principles and clinical prospects. *Radiology* **289**, 293–312 (2018).
142. Weese, J. & Lorenz, C. Four challenges in medical image analysis from an industrial perspective. *Med. Image Anal.* **33**, 44–49 (2016).
143. Hutter, F., Kotthoff, L. & Vanschoren, J. (eds) *Automated Machine Learning: Methods, Systems, Challenges* (Springer, 2019).
144. Minter, S. et al. Crowdsourcing consensus: proposal of a novel method for assessing accuracy in echocardiography interpretation. *Int. J. Cardiovasc. Imaging* **34**, 1725–1730 (2018).
145. Pace, D. F. et al. Interactive whole-heart segmentation in congenital heart disease. *Med. Image Comput. Comput. Assist. Interv.* **9351**, 80–88 (2015).
146. Chen, L. et al. Self-supervised learning for medical image analysis using image context restoration. *Med. Image Anal.* **58**, 101539 (2019).
147. Arafati, A. et al. Artificial intelligence in pediatric and adult congenital cardiac MRI: an unmet clinical need. *Cardiovasc. Diagn. Ther.* **9** (Suppl. 2), S310–S325 (2019).
148. Chartsias, A. et al. Disentangled representation learning in cardiac image analysis. *Med. Image Anal.* **58**, 101535 (2019).
149. Sengupta, P. P. et al. Proposed requirements for cardiovascular imaging-related machine learning evaluation (PRIME): A checklist: reviewed by the American College of Cardiology Healthcare Innovation Council. *JACC Cardiovasc. Imaging* **13**, 2017–2035 (2020).
150. Barredo Arrieta, A. et al. Explainable artificial intelligence (XAI): concepts, taxonomies, opportunities and challenges toward responsible AI. *Inf. Fusion.* **58**, 82–115 (2020).
151. Cabitza, F., Rasoini, R. & Gensini, G. F. Unintended consequences of machine learning in medicine. *JAMA* **318**, 517–518 (2017).
152. European Commission. Ethics guidelines for trustworthy AI. *European Commission* https://ec.europa.eu/digital-single-market/en/news/ethics-guidelines-trustworthy-ai (2019).
153. Recht, M. P. et al. Integrating artificial intelligence into the clinical practice of radiology: challenges and recommendations. *Eur. Radiol.* **30**, 3576–3584 (2020).

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