performed a cognitive ML using STE data and found that a cognitive ML (15 STE variables and the 4 echo variables) was superior to e′ (medial mitral annular early diastolic velocity) and longitudinal strain for differentiating constrictive pericarditis from restrictive cardiomyopathy, compared with random forests and support vector machines. Briefly, ML can be broken down into supervised and unsupervised. In supervised learning, ML algorithms use a human hand-coded dataset to predict the desired outcome. In contrast, unsupervised learning seeks to find hidden patterns in the data to identify novel disease mechanisms. For example, Shah et al. (4) performed unsupervised learning to identify intrinsic structure within heart failure with preserved ejection fraction patients and they could identify 3 different phenotypes and subsequently performed supervised learning to predict the difference of desired outcomes (mortality and hospitalization) among those 3 groups.

Deep learning (DL), which mimics how the human brain works, can generate predictions from an input training dataset based on the use of multiple hidden layers. DL has become a hot topic in ML because: 1) it can be very powerful in image recognition (i.e., facial recognition in Facebook or image search in Google); 2) it can be trained in an unsupervised manner for unsupervised learning tasks; 3) there is no limit in working memory; and 4) it can work well with noisy data such as strain imaging and 3-dimensional STE. However, the downside of DL is that: 1) overfitting might become a more significant issue compared with classical ML; 2) it requires large datasets to work well; and 3) it takes time to set up a neural network using DL algorithms.

To date, the implementation of DL with unsupervised feature in echocardiographic imaging is still in its infancy, but appears promising. Therefore, we suggest that unsupervised DL with STE data might identify novel phenotypes of cardiomyopathy, with potential toward precision of cardiovascular medicine.

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## REPLY: Deep Learning With Unsupervised Feature in Echocardiographic Imaging

We would like to thank Dr. Krittanawong and colleagues for the encouraging comment about our work on introducing machine learning for artificial intelligence (AI)-aided interpretation of cardiac imaging. The authors make an interesting proposition through introducing the emerging concept of deep learning (DL) as a means of automating phenotyping and recommendation tasks in echocardiography and cardiology more broadly.

DL represents a class of algorithms based on artificial neural networks, and it can handle raw data without defining variables a priori—a technique called feature representation. This is particularly well suited for large, diverse, and complex datasets with thousands of samples. However, our machine learning framework was constructed with the goal of both optimal prediction and identification of key inputs driving the classification (1,2). As a model benchmarked using pre-determined speckle tracking variables, supervised machine learning models were more appropriate for our particular tasks. Implementing DL on small samples (e.g., in our study <100 samples per class) may lead to overfitting—a phenomenon in which the model fits your current data well but does not predict well with unseen cases. DL is ideal for studies with a large number of samples and data points. For example, in a recent study by Miotto et al. (3) using data from 700,000 patients with 60,238 clinical variables, we were able to accurately predict future incidence of disease sequelae. In another study, we used Bayesian modeling on 1,068 patients to predict the probabilities of unplanned hospital readmission rates in heart failure patients using 105 features (4). Thus, the choice of algorithms and the success of implementations depend on many elements including sample size, formulation of predictive modeling, data completeness, and evidence from orthogonal validations.

DL has shown major success in learning from video data (e.g., echo data as a stream of images) in an active AI subfield known as computer vision. As DL capabilities improve with novel models including generative adversarial networks and value iteration networks, we envisage that DL can be applied to diagnostic imaging and AI-based predictions at the point of care in cardiology. However, all these techniques, whether they fall under the broad categorization of machine learning, DL, cognitive computing, or computer vision, are all subsets of AI and are an attempt to move closer to more widespread implementation of smart clinical decision systems capable of either diagnosing or aiding the clinician in making a diagnosis. We certainly agree with the remarks about DL; however, in our example of classifying physiological from pathological hypertrophy, a simpler learning approach using ensemble learning with artificial neural networks and more shallow classifiers was effective. In conclusion, as our databases continue to grow in both sample size and number of features, our models will continue to increase in complexity.

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