METHODIST DEBAKEY CARDIOVASCULAR JOURNAL

Role of Artificial Intelligence and Machine Learning to Create Predictors, Enhance Molecular Understanding, and Implement Purposeful Programs for Myocardial Recovery

REVIEW

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ABSTRACT

Heart failure (HF) affects millions of individuals and causes hundreds of thousands of deaths each year in the United States. Despite the public health burden, medical and device therapies for HF significantly improve clinical outcomes and, in a subset of patients, can cause reversal of abnormalities in cardiac structure and function, termed "myocardial recovery." By identifying novel patterns in high-dimensional data, artificial intelligence (AI) and machine learning (ML) algorithms can enhance the identification of key predictors and molecular drivers of myocardial recovery. Emerging research in the area has begun to demonstrate exciting results that could advance the standard of care. Although major obstacles remain to translate this technology to clinical practice, AI and ML hold the potential to usher in a new era of purposeful myocardial recovery programs based on precision medicine. In this review, we discuss applications of ML to the prediction of myocardial recovery, potential roles of ML in elucidating the mechanistic basis underlying recovery, barriers to the implementation of ML in clinical practice, and areas for future research.

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KEYWORDS:
heart failure; myocardial recovery; reverse remodeling; machine learning; artificial intelligence; omics

TO CITE THIS ARTICLE:
Lang FM, Lee BC, Lotan D, Sabuncu MR, Topkara VK. Role of Artificial Intelligence and Machine Learning to Create Predictors, Enhance Molecular Understanding, and Implement Purposeful Programs for Myocardial Recovery. Methodist DeBakey Cardiovasc J. 2024;20(4):76-87. doi: 10.14797/mdcvj.1392

INTRODUCTION

Heart failure (HF) is a heterogeneous clinical syndrome resulting from altered hemodynamics, disrupted fluid balance, and maladaptive biochemical changes driven by a structural or functional impairment in cardiac ejection or filling.[1,2] Heart failure is a major public health challenge, affecting over 6 million people and causing hundreds of thousands of deaths each year in the United States.[3] Despite the societal burden, medical and device therapies for HF have dramatically advanced over the past several decades, capable of significantly improving clinical outcomes. It is now well-recognized that guideline-directed medical therapy (GDMT), cardiac resynchronization therapy (CRT), valvular interventions, and mechanical circulatory support can slow or even reverse the progressive abnormalities of cardiac structure and function observed in HF, termed reverse remodeling and/or "myocardial recovery."[4,5] Myocardial recovery has been associated with more favorable outcomes than typical HF cases, prompting the creation of a new category of HF, heart failure with improved ejection fraction (HFimpEF), in the 2022 HF management guidelines.[1,6,7] These observations have driven significant research into the mechanistic basis of myocardial recovery, with the goal of identifying therapeutic strategies that can augment or induce recovery de novo in patients with HF.

Artificial intelligence (AI) and machine learning (ML) have become increasingly integrated into the public sphere over the past decade. AI refers to computer systems that can perform tasks that have historically required human intelligence. ML, a subset of AI, encompasses the development and use of algorithms that allow computers to draw inferences from data without explicit instructions.[8,9] Whereas use cases for ML have previously focused on automating pattern-heavy tasks to replace the human worker with a computer, ML is now increasingly being used to recognize novel patterns in data that cannot be identified by humans, even those with significant domain expertise. The application of ML to large datasets derived from patients with HF has the potential to uncover key drivers of myocardial recovery that may dramatically alter clinical practice and drug development.[10] In this review, we discuss the applications of ML to HF, the use of ML for predicting myocardial recovery and enhancing cardiac "-omic" analyses, barriers impeding the translation of ML to clinical cardiology, and potential areas for future research to promote the successful implementation of purposeful myocardial recovery programs (Figure 1).

MACHINE LEARNING BASICS AND APPLICATIONS TO HEART FAILURE

FUNDAMENTAL CONCEPTS IN MACHINE LEARNING

In contrast to traditional algorithms that apply predefined rules to input data to generate outputs, ML algorithms analyze input and output data to generate rules for creating new outputs (Figure 2A).[8] Thus, ML algorithms can learn from data (training dataset), and the learned rules (the ML model) can be applied to new datasets (test dataset) without requiring manual coding changes from a human. Larger and more diverse training datasets are preferable as they allow ML models to work well when applied to a greater variety of novel test datasets. Compared with traditional statistical methods (eg, linear/logistic regression), ML algorithms are advantageous because they can handle nonlinear nonprespecified interactions and retain strong performance when processing data containing a high number of variables (high-dimensional data).[9]

Machine learning algorithms can generate models via two main learning methodologies: supervised or unsupervised (Figure 2B). Supervised learning occurs under the condition that the training dataset is "labeled," meaning each input is associated with a prespecified output. The advantage of this approach is that the algorithm focuses on understanding a specific variable of interest and generally needs less data to create a robust model.[8,9] The disadvantage is that the process of labeling data can be error-prone and time-intensive, potentially requiring manual interpretation of raw data by a human expert. In contrast, unsupervised learning is performed on unlabeled training data. The ML algorithm identifies which datapoints are similar and clusters them into different groups based on those similarities. The advantage of unsupervised learning is that hidden patterns in data can be identified, circumventing preexisting human biases that would have inherently affected the labeling process. The disadvantage is that interpreting the meaning of clusters can be challenging, potentially limiting real-world applicability of results.[9] Further, more training data is often required to generate a robust model given the lack of direction to guide analysis.[9] Beyond supervised and unsupervised learning, it is important to note that other advanced learning methods have been developed, such as "deep learning" that uses neural networks to process data across multiple layers of nodes.[9]

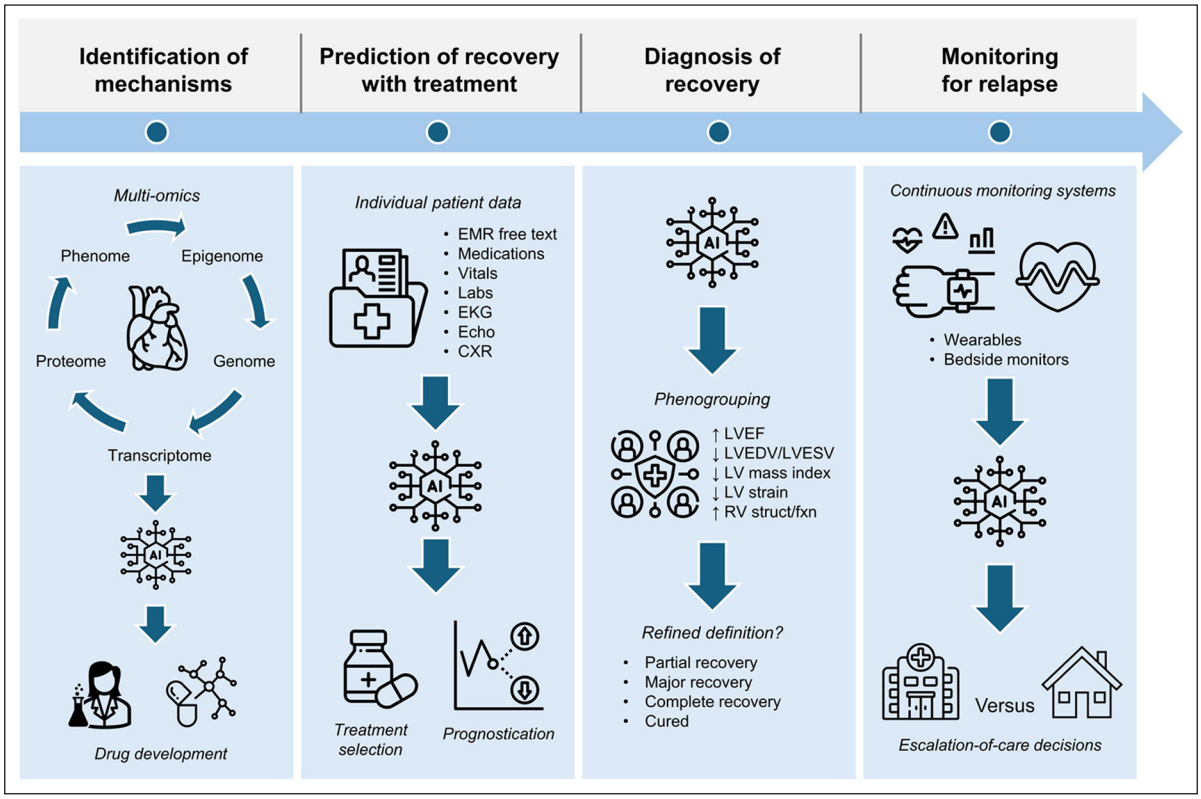

Figure 1 Incorporation of artificial intelligence (AI) and machine learning (ML) into research and clinical workflows to achieve successful implementation of purposeful myocardial recovery programs. ML could be applied to multi-omic datasets to elucidate novel drivers of myocardial recovery and accelerate drug development. ML could process vast amounts of individual patient data to predict chances of recovery with tailored treatment regimens. ML could create new heart failure phenogroups that better delineate prognostically important thresholds for changes in myocardial structure and function, thereby allowing for a refined definition of recovery that incorporates a spectrum of phenotypes from partial recovery to cure. In a patient who has recovered, ML could track data from high-volume continuous monitoring systems to identify candidates who need escalation of care to prevent relapse. Icons were obtained from flaticon.com. CXR: chest x-ray; Echo: echocardiography; EKG: electrocardiogram; EMR: electronic medical record; LV: left ventricular; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; RV struct/fxn: right ventricular structure and function

APPLICATIONS OF MACHINE LEARNING TO UNDERSTAND, DIAGNOSE, AND MANAGE HEART FAILURE

Numerous studies have applied ML algorithms to the field of HF, and they have been the subject of several reviews.[8–11] Specifically, ML techniques have been used to support the diagnosis of HF,[12–16] improve risk stratification for adverse outcomes,[17–24] create novel HF classifications,[25–27] predict prognosis after treatment,[28–31] strengthen continuous monitoring systems,[32,33] and perform automated interpretation of diagnostic studies.[34–36] Results from some of these algorithms have demonstrated superiority over results derived from traditional methods, including the widely-used Pooled Cohort Risk Equation[18] and MAGGIC mortality risk score.[19] Likewise, diagnostic performances of ML models have been shown to be superior to general cardiologists and cardiology residents for HF diagnosis and arrhythmia classification, respectively[14,35] Similarly, our group recently used supervised learning to develop an ML model demonstrating superior diagnostic performance to radiologists for recognizing a dilated or hypertrophied left ventricle (LV) on chest x-ray.[16] Together, these studies demonstrate the broad applications of ML for improving the care of HF patients and indicate that translation of research findings to clinical practice may be on the horizon.

MACHINE LEARNING IN PREDICTION OF MYOCARDIAL RECOVERY

FORMS OF MYOCARDIAL RECOVERY AND ASSOCIATED OUTCOMES

Clinical studies have demonstrated that device and medical therapies (ie, beta-blockers, renin-angiotensin-aldosterone system inhibitors, and sodium-glucose cotransporter-2 inhibitors, or SGLT2i) proven to prolong life in HF patients can result in reverse remodeling and myocardial recovery.[5,37] Some etiologies of HF with reduced ejection fraction (HFrEF), including myocarditis, peripartum cardiomyopathy, and tachyarrhythmia, are more likely to

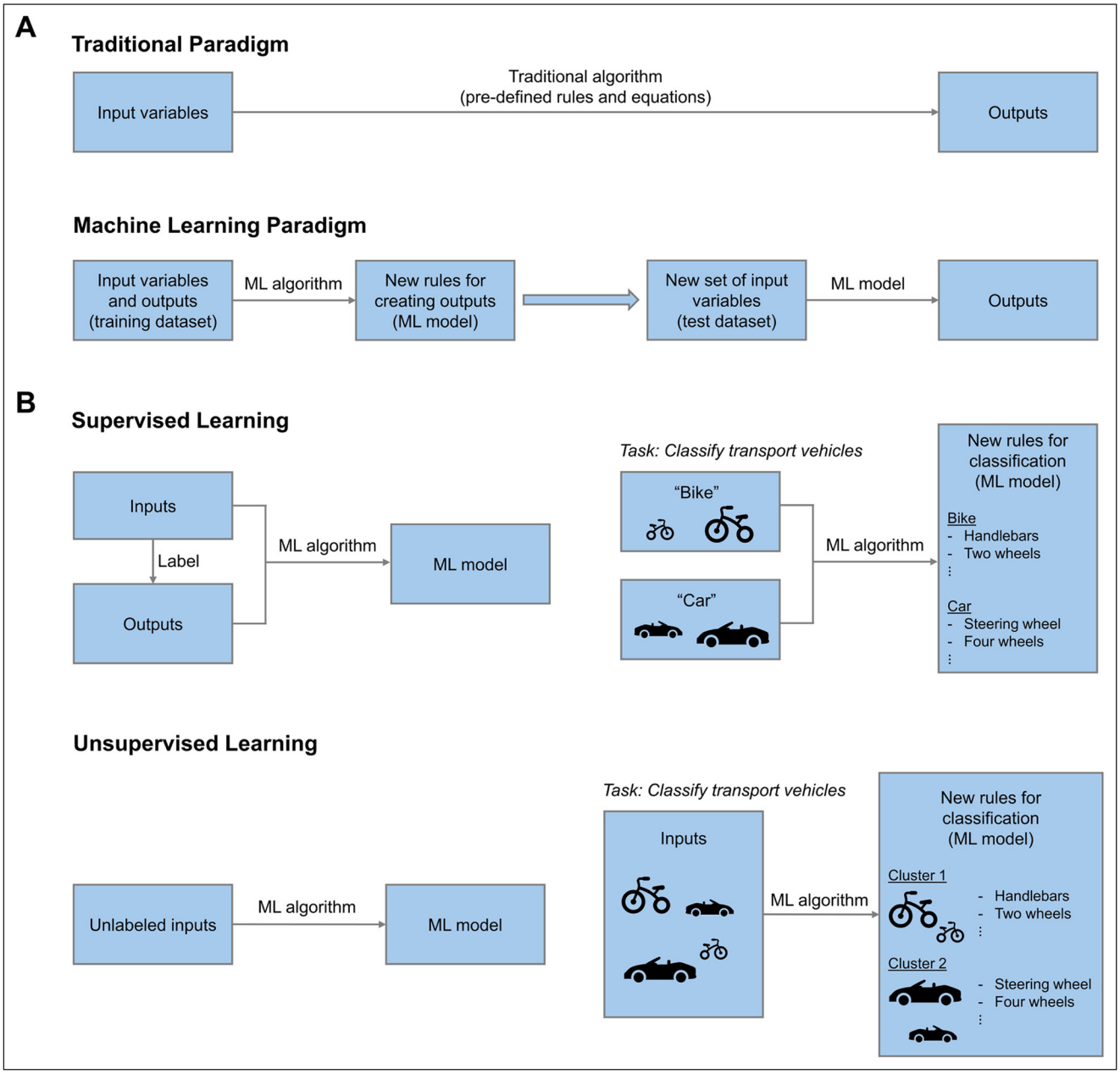

Figure 2 Differences between **(A)** traditional algorithms and machine learning (ML) algorithms and **(B)** supervised and unsupervised learning. Traditional algorithms apply predefined rules to input data, whereas ML algorithms create rules from training data to apply to new test data without human intervention. Supervised learning utilizes labeled data to train the ML model. When training a model to perform a task of classifying transport vehicles into bikes and cars, an ML algorithm will identify the key features comprising a bike versus a car and develop a set of rules for classification of each. Unsupervised learning trains the model on unlabeled data. An unsupervised ML algorithm training a model to classify transport vehicles into bikes and cars will cluster the data into groups with similar features, generating a set of rules for classification of each group. "Bikes" and "cars" are not explicitly named, but successful clustering will have properly separated out the two types of vehicles

recover than others[5]; however, myocardial recovery is not always sustained as patients can relapse after initially major clinical and/or echocardiographic improvement.[38] Further, the incidence of recovery varies from < 1% to 40% across HF etiologies, disease severities, study designs, and selected definitions.[5,38,39] Myocardial recovery as defined by normalization or near-normalization of LV ejection fraction (LVEF)—known as "functional recovery" or HF with improved EF (HFimpEF)—is prognostically significant, associated with lower rates of HF hospitalizations and mortality.[5–7] Myocardial recovery as defined by improvements in LV end-systolic volume and end-diastolic volume after treatment ("structural recovery") have been directly correlated with mortality risk reduction in HFrEF.[40]

Perhaps, the most striking form of myocardial recovery is the reversal of chronic ventricular dilation and achievement of left ventricular assist device (LVAD) explantation in patients with end-stage HFrEF, which is associated with robust outcomes similar to transplanted patients.[24,38,39,41,42] Ultimately, myocardial recovery can take many forms but is generally associated with favorable outcomes regardless of the definition used.

TRADITIONAL PREDICTORS OF MYOCARDIAL RECOVERY

Given the prognostic significance, prediction of myocardial recovery is clinically useful. Traditional statistical methods have established several key factors associated with recovery. Across studies of all-comer HF patients, factors associated with HFimpEF included young age, nonischemic cardiomyopathy, female sex, shorter duration of HF, lower comorbidity burden, more intensive GDMT use, and lower levels of NTproBNP and troponin.[5–7,43–46] In studies of end-stage patients on LVAD, factors associated with device explantation were largely similar, including young age, nonischemic cardiomyopathy, shorter duration of HF, and more intensive GDMT use while implanted.[38,39,41,47–50] Interestingly, these studies demonstrated that many LVAD patients who achieved substantial improvement in LVEF did not undergo explantation, likely because such patients were not selected a priori for a bridge-to-recovery strategy, which commits the clinical team to close monitoring over time and significantly increases explantation rates.[38,50,51] These findings highlight the importance of identifying candidates for recovery early, and regression-based recovery prediction scores, such as Complete Recovery Score by the Columbia Group (I-TOPS)[49] and INTERMACS including Cardiac Recovery Score (I-CARS),[50] have been developed for this purpose.

APPLICATION OF MACHINE LEARNING TO PREDICT MYOCARDIAL RECOVERY

Given its advantages over traditional statistical methods, ML represents a powerful tool for improving myocardial recovery prediction across the spectrum of HF. Significant ML-based research has already been undertaken to understand recovery after CRT implantation. Using randomized trial data, Cikes et al. were the first to apply ML techniques to identify responders and nonresponders to CRT.[52] The authors utilized unsupervised learning to define four phenogroups of patients with distinct baseline echocardiographic characteristics, medical histories, and medication use. Only two phenogroups exhibited significant improvements in event-free survival with CRT. These two phenogroups also demonstrated greater evidence of structural recovery with CRT than the other phenogroups. Typical characteristics of the two phenogroups included young age, nonischemic cardiomyopathy, female sex, left bundle branch block, and septal flash pattern.[52] More recently, new studies have built on these findings by utilizing ML techniques applied to different input variables and response/recovery definitions.[53–59] Ultimately, these studies demonstrate the power of ML, particularly unsupervised learning, for creating unique HF classifications with differential potential for myocardial recovery after device treatment.

Several studies have applied supervised ML to predict myocardial recovery with GDMT in HFrEF. MacGregor et al. utilized ML analysis of cardiac magnetic resonance imaging from patients with idiopathic dilated cardiomyopathy to predict response to medical therapy, defined as symptom improvement and increase in LVEF > 10%.[60] The resulting ML model relied most on regional LV strain measurements and discriminated responders and nonresponders with an impressive area under curve (AUC) of 0.94. Similarly, Mohebi et al. applied ML to understand LVEF improvement to ≥ 35% after sacubitril/valsartan treatment.[61] Lower HF duration and less extensive LV remodeling (eg, higher LVEF and lower LV mass index) were associated with greater probability of recovery. The ML model was able to predict lack of recovery at 1 year with an AUC of 0.86 in a test dataset. Finally, Mele et al. studied diabetic HFrEF patients treated with SGLT2i and identified several baseline echocardiographic characteristics, such as tricuspid annular plane systolic excursion, to be important for the prediction of structural/functional LV improvements after treatment.[62] Given that all GDMT classes can induce myocardial recovery, these studies demonstrate emerging applications of ML to better understand the heterogeneous responses to GDMT in patients with stable HFrEF.

Leveraging the INTERMACS dataset of > 20,000 patients, our group was the first to apply ML to understand predictors of LVAD explantation.[63] Here, LASSO (least absolute shrinkage and selection operator) feature selection was first used to identify 28 clinical variables correlated with recovery, including smoking, alcohol use, and medication nonadherence, which were not identified in prior regression-based studies. These variables were then fed into five ML algorithms, and all resulting ML models had significantly better predictive ability (AUCs > 0.810) than previously published I-TOPS and I-CARS scores ($P < .001$).[49,50] The best-performing ML model demonstrated significantly superior performance to an updated prediction score derived from traditional statistical methods applied to the contemporaneous INTERMACS dataset ($P = .046$).[63] Patients who were predicted to recover by ML demonstrated lower mortality and greater chance of LVEF recovery on LVAD support. Interestingly, the identification of substance use

and medication nonadherence as positive predictors of recovery seemed counterintuitive, but our group surmised that patients with such characteristics were less likely to be listed for transplant, increasing time on LVAD support and thus chances of recovery. It is also plausible that some nonadherent patients become motivated to change their habits after LVAD implantation.[63] Overall, this supervised learning-based study identified previously unappreciated predictors of recovery and demonstrated that ML can improve clinical decision-making around candidacy selection for LVAD recovery.

Finally, Adekkanattu et al. were the first to apply ML to an unstructured dataset of electronic medical records (EMR) from > 40,000 patients to predict LVEF changes over time.[64] Several ML models were developed and demonstrated AUCs of ~0.85 to 0.90 for predicting an increase in LVEF ≥ 30% at 1 year. The most important predictive features were initial EF, age, ischemic heart disease, chronic obstructive pulmonary disease, and hypertension. This study demonstrated the feasibility of mining EMR data with ML to understand the likelihood of myocardial recovery.

MACHINE LEARNING TO ENHANCE MOLECULAR UNDERSTANDING IN MYOCARDIAL RECOVERY

EMERGING MOLECULAR MARKERS ASSOCIATED WITH MYOCARDIAL RECOVERY

Identification of mechanistic drivers of recovery may aid the development of new therapeutic strategies. By going beyond clinical predictors, novel molecular markers associated with recovery have begun to emerge. Proteins involved in myocardial fibrosis, including soluble suppression of tumorigenesis-2 (sST2),[65] galectin-3,[66] and procollagen type I c-terminal propeptide (PICP),[67] have been directly correlated with adverse cardiovascular outcomes and inversely correlated with improvements in LV structure/function. Inflammatory cytokines, namely interferon-γ and tumor necrosis factor-α, have been inversely correlated with recovery.[68] Specific gene signatures, as well as expression of certain mRNAs, microRNAs, and long non-coding RNAs, have been associated with recovery in mouse models of reversible HF as well as in studies evaluating recovered, failing, and nonfailing human heart tissue.[69–72] Recently, our group has shown that the epigenetic profile of failing hearts could help determine HF etiology and chances of myocardial recovery on LVAD support.[73] Lastly, a study of patients on LVAD brought together transcriptomic and proteomic datasets ("multi-omics"), identifying differential expression of 17 cell cycle-related transcripts/peptides and 22 extracellular matrix-related transcripts/peptides associated with recovery, most of which were novel.[74] As the genomic, transcriptomic, proteomic, and epigenomic datasets from HF patients become increasingly advanced and well-integrated with clinical datasets, the molecular underpinnings of myocardial recovery can be better elucidated.

ROLE OF MACHINE LEARNING TO IDENTIFY MOLECULAR MARKERS ASSOCIATED WITH RECOVERY

Due to the high dimensionality of -omic datasets, -omic analyses have been limited by traditional statistical methods relying on thousands to millions of pairwise t-tests that are rarely significant after adjusting for multiplicity. Further, these traditional methods cannot account for nonlinear relationships that are invariably present. ML techniques represent a more sophisticated methodology for deriving novel insights from these complex datasets.

ML algorithms have begun to be applied to -omic datasets from HF patients, revealing new pathophysiologic insights. Ouwerkerk et al. created an ML model derived from 6 million genomic markers, 403 proteins, 36046 transcripts, and 54 clinical variables to predict mortality in patients with HF.[75] The most predictive features in the model were WFDC2 protein level, history of renal disease, TRAIL-R2 protein level, and TRAJ16 transcript level. Four major molecular pathways were identified as activated during HF progression and GDMT underdosing: PI3K-Akt signaling, MAPK signaling, RAS signaling, and EGFR tyrosine kinase inhibitor resistance. Similarly, de Bakker et al. used ML to analyze large proteomic and clinical datasets to predict HF hospitalization and cardiovascular death in patients with HFrEF.[76] ML techniques identified 9 out of 4210 serially-measured proteins as prognostically significant on top of established risk factors, with the resulting model demonstrating strong predictive ability (*c*-index 0.80) in a test dataset.[76] These exciting analyses demonstrate the power of ML to comprehensively analyze -omic datasets for the identification of novel molecular drivers of HF progression.

To our knowledge, ML algorithms have not been applied to -omic datasets in the context of research questions related to myocardial recovery. Given that ML has already been applied to understand HF progression, similar methodologies could be applied to understand recovery from HF. The use of ML to correlate improvements in functional/structural LV measurements with changes in protein, transcript, genetic, and epigenetic markers over time holds significant potential for identifying recovery-driving molecular pathways that could be targeted by novel therapeutic agents.

BARRIERS TO UNLOCKING THE FULL POTENTIAL OF MACHINE LEARNING

The application of ML to the care of patients with HF remains an emerging area of research.[10] A PubMed search of "heart failure" plus "artificial intelligence" or "machine learning" yielded only ~1,600 results, with over 80% of the articles being published in the past 5 years. Significant work remains to successfully translate ML to clinical use, particularly in the area of myocardial recovery.

Despite the successes discussed in this review, several studies that relied on ML analysis of tabular datasets have produced only modest improvement over results derived from traditional statistical methods.[24,63,76,77] Wehbe has proposed that these observations are not a shortcoming of ML but, rather, a limitation inherent in the application of ML to structured data.[77] ML techniques, particularly deep learning, have the advantage of being able to process unstructured data, including raw images and EMR free text. Encouraging results from ML analyses of unstructured data have already been reported, and expansion of large-scale registries to include unstructured data may unlock the full capabilities of ML to identify novel patterns that enhance HF care.[16,64,77]

Constraints inherent to provider adoption represent another barrier to the clinical translation of ML. Currently, decision-making tools such as risk scores usually require manual data input by the clinician using an online calculator. Simple tools with less than five to seven input variables are preferred by busy clinicians,[78] but most ML models use many more variables to optimize performance. To address these competing priorities, ML models would need to be integrated within the EMR, such that patient data is automatically pulled into the models and results are displayed to the clinician in an easily-readable graphical user interface. However, EMR integration of ML holds significant technical, logistical, and regulatory challenges, including the need for securitized protected health information and the potentially significant loss of model performance from spurious or unavailable inputs in real-world situations.[79]

Another concern is the potential to create biased models that exacerbate healthcare disparities. If an ML model's training dataset underrepresents certain populations, the model will likely demonstrate worse performance when externally applied to those populations, thereby creating racial, gender, and socioeconomic biases that could worsen outcomes of already marginalized patients. Importantly, major government-funded genomic datasets have been reported to be only about 4% non-European, demonstrating the bias inherent in even commonly-used resources.[10] Creation of large diverse training datasets is essential for the fair development of ML models.

Lastly, limited interpretability is an important barrier. Many ML algorithms are termed "black-box" because the developer cannot fully explain how the model arrives at its output. Lack of clarification leads a clinician to mistrust a model's results, particularly if the model's conclusion differs from the clinician's intuition. To increase trust, use of explainability tools (eg, feature importance graphs) alongside ML outputs will be critical.[31,77] Further, F1 scores are often used in computer science to describe the predictive power of ML models. However, such scores are less interpretable than traditional AUC with sensitivity, specificity, and positive/negative predictive value, which are intuitively applicable by clinicians. Thus, authors of ML-based studies should make significant efforts to ensure model explainability and performance interpretability to improve real-world actionability.

AREAS FOR FUTURE RESEARCH

The application of ML to myocardial recovery presents numerous exciting areas for future study (Figure 1). Many large observational registries, clinical trial datasets, and biorepositories have been extensively mined using traditional statistical methods but are now ripe for analysis by ML techniques.

Currently, all patients with HFrEF are trialed on the same four pillars of GDMT derived from population-level studies.[1] However, HFrEF is a heterogenous disease with numerous etiologies, and individual patients may respond differently to each therapy. Likewise, many device therapies carry broad indications but have variable responses after implantation. Even the definition of HFimpEF, the only guideline-endorsed classification of HF that incorporates some form of myocardial recovery, is relatively simple, comprised of LVEF alone alongside somewhat arbitrary LVEF improvement thresholds that differ across society guidelines.[1,80]

Through ML analysis of multi-omic data from HF patients who have achieved myocardial recovery, essential molecular pathways driving recovery can be uncovered to accelerate drug development. By better predicting chances of myocardial recovery across clinical scenarios, ML can help identify candidates for therapy earlier, particularly in challenging situations, such as proceeding with LVAD or heart transplant in a young patient with cardiogenic shock. Further, prediction of individual patient responses to specific HF therapies could allow for personalized treatment that minimizes polypharmacy, decreases drug

side effects, avoids unnecessary device implantations, and improves outcomes. Finally, through identification of new prognostically important phenogroups, ML can help develop a more refined definition for "recovered HF" that incorporates key indices of LV structure/function beyond LVEF, allowing for improved monitoring, patient counseling, and treatment selection to prevent HF relapse.

In this review, we have cited several studies demonstrating proof-of-concept that such goals are within reach in the coming years. Further research is needed to transform proof-of-concept tools into validated clinical products.

CONCLUSION

AI and ML have enormous potential to usher in a new era of purposeful myocardial recovery programs tailored to each patient's specific needs. Emerging research has shown that ML tools can enhance our ability to predict and understand myocardial recovery across the spectrum of HF. However, widespread adoption of ML in the clinic has yet to occur. Barriers to clinical translation include limited availability of unstructured datasets, rigorous requirements for provider adoption, potential for demographic bias, and insufficient model interpretability. Areas for future ML-based research in myocardial recovery include treatment response prediction, risk stratification, refined phenogrouping, and multi-omic dataset utilization. The proper application of ML tools to high-dimensional datasets will help clinicians achieve myocardial recovery in a more diverse group of HF patients than ever before.

KEY POINTS

- In a subset of patients with heart failure (HF), medical and device therapies can reverse abnormalities in cardiac structure and function, a phenomenon known as "myocardial recovery."
- Artificial intelligence and machine learning (ML) algorithms allow computers to identify novel patterns in high-dimensional data and are superior to traditional statistical methods for handling complex interactions in large datasets.
- Emerging research has demonstrated the feasibility of applying ML to understand and predict myocardial recovery with pharmacologic and device therapies, such as guideline-directed medical therapy, cardiac resynchronization therapy, and mechanical circulatory support, across the spectrum of HF.
- ML has yet to be translated to the clinic at significant scale, owing to barriers such as limited availability of unstructured datasets, rigorous requirements for provider adoption, bias in training datasets, and difficulties surrounding model interpretability.
- By improving mechanistic understanding, treatment response prediction, phenogrouping, and monitoring, ML has the potential to usher in a new era of purposeful programs for myocardial recovery.

ACKNOWLEDGEMENTS

The authors thank Alexandre Barbet, an industry expert in machine learning, for his assistance in describing key machine learning concepts.

COMPETING INTERESTS

FML reports no conflicts related to this work. Outside of this work, FML reports equity options in Roivant Sciences and consulting fees from Roivant Sciences and Kinevant Sciences. VKT is supported by National Institutes of Health grant HL170132. The other authors have no conflicts to disclose.

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TO CITE THIS ARTICLE:
Lang FM, Lee BC, Lotan D, Sabuncu MR, Topkara VK. Role of Artificial Intelligence and Machine Learning to Create Predictors, Enhance Molecular Understanding, and Implement Purposeful Programs for Myocardial Recovery. Methodist DeBakey Cardiovasc J. 2024;20(4):76-87. doi: 10.14797/mdcvj.1392

Submitted: 10 April 2024 **Accepted:** 23 May 2024 **Published:** 20 August 2024