Characterizing mitral regurgitation with precision phenotyping and unsupervised learning

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Secondary mitral regurgitation (MR) is a complex disease with many etiologies leading to different physiology, anatomy, and response to intervention. With the adoption of new technologies and techniques seeking to percutaneously repair mitral regurgitation, there has been renewed interest in re-evaluating the disease and identifying patients that might benefit from percutaneous interventions. Diverging results from randomized trials of the same technology highlight the importance of patient selection and phenotyping in characterizing MR. In this manuscript, Bartko et al use unsupervised machine learning and clustering techniques to study patient subpopulations with secondary MR [1]. From a cohort of patients recruited from single high-volume medical center's heart failure clinic, the authors used principal component analysis on quantitative variables from echocardiography as well as the patient's clinical characteristics to identify phenotypic subgroups.

In this manuscript, the authors used unsupervised machine learning techniques to cluster similar patients into phenotypic groups then shown to have different outcomes. By collecting and organizing a large set of high-dimensional data and performing principal component analysis, the authors did not pre-specifying the phenotypic groupings, but rather allowed the measurements themselves to identify the most relevant features that distinguish and classify each group. Principal component analysis identifies the most relevant components (features or measurements) that help distinguish between groups and clusters patient into a few main phenotypic groups based on these key metrics. In this analysis, features were divided into measurements related to the atria, mitral valve, and the left ventricle as the most important components.

From this analysis, the authors highlight the importance of identifying the degree of secondary MR out of proportion to the degree of ventricular dysfunction. In particular, atrial anatomic indices out of proportion to left ventricular indices (represented as either large left atrium or small ventricular cavity) and a high regurgitant fraction with a small ventricle has a significant impact on clustering patients into phenotypic groups with differential mortality. This difference in ventricular size found from unsupervised clustering could explain differences in efficacy between the MITRA-FR and COAPT trials [2,3]. Important changes in the left atrium as well as the mitral apparatus help shape the type and severity of MR present. The ability for such anatomic metrics to influence mortality highlight both opportunities for early intervention as well as the natural progression and remodeling of secondary MR.

Although these results are promising, expert clinician judgement and evaluation continues to be critical for medical decision making, particularly for complex cases of MR.

As with all forms of data analysis, the quality of the underlying data is key – particularly when subsequently used for machine learning and principal component analysis. With multiple methods to calculate critical metrics of MR as well as the dependency on expert image acquisition, the underlying metrics can vary with eccentric regurgitation, duration of MR during the cardiac cycle, and having multiple jets of MR. Notably, most of the features for model prediction are primarily anatomic. Important clinical features, such as the presence of atrial fibrillation and whether the left ventricular systolic dysfunction was global or regional are known to affect the severity of MR [4], but not included in the analyzed feature set. It is also unclear how patients who underwent surgical or percutaneous mitral interventions were handled here. Such interventions could alter the natural history, but to exclude them would also be biasing. A frequently repeated but important point is recognized by the authors – that association does not prove causation, and in a progressive disease, anatomic features (such as atrial enlargement) could be both the cause and result of time-dependent remodeling.

With this information, clinicians can identify if the patients before them map to the four main phenotypic clusters identified by the authors. Releasing their code, Bartko et al's analysis allows for cardiologists to identify how their particular patient fit into the space of many different physiologies of secondary MR and if the predicted mortality would warrant earlier intervention. The release of code should be encouraged and applauded, as increasingly complex methodologies are being used to analyze medical imaging [6] and reproducibility depends on sharing code, model weights, and imaging data when possible. Tremendous progress has been made in computer science and artificial intelligence over the last two decades, and much of that progress relies on the relative ease to build upon the work of others and rapidly innovate with open sharing of information.

This study is quite timely as there is rapid advancement in the technologies for percutaneous intervention for mitral regurgitation. With similar inclusion criteria, patient ages, New York Heart Association class, rates of procedural success, and primary endpoints, the MITRA-FR and COAPT trials highlight how imaging features and improved patient selection could significant impact the outcomes of patients with concomitant heart failure and valve disease [2,3]. From their analysis, Bartko et al suggest the two trial populations might be better classified into separate phenotypes of secondary MR, explaining the lack of anticipated benefit of percutaneous intervention in MITRA-FR that was seen in COAPT, an evolution of the concept of "disproportional MR" expressed by Grayburn et al. [5]. While there is tremendous opportunity for improving patient care, two landmark randomized, controlled trials for MitraClip highlight the importance of patient selection and the increasing need to understand and phenotype MR. With the increasing availability of percutaneous options, large scale data analysis on the natural history of MR might no longer be as easily obtained. Ultimately, randomized controlled trials will be needed to understand the causal impact of percutaneous therapies and optimal strategies to choose the patients most benefiting from intervention for secondary MR.

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