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ORIGINAL RESEARCH

EMERGING TECHNOLOGIES

Thoracic Aortic Aneurysm Risk Assessment

A Machine Learning Approach

Lauren Kennedy, MSc,[a,b] Kevin Bates, MSc,[a,b] Judith Therrien, MD,[c] Yoni Grossman, MD,[c] Masaki Kodaira, MD,[c] Josephine Pressacco, MD, PhD,[d] Anthony Rosati, BEng,[a,b] François Dagenais, MD,[e] Richard L. Leask, PhD,[a] Kevin Lachapelle, MD[b]

ABSTRACT

BACKGROUND Traditional methods of risk assessment for thoracic aortic aneurysm (TAA) based on aneurysm size alone have been called into question as being unreliable in predicting complications. Biomechanical function of aortic tissue may be a better predictor of risk, but it is difficult to determine in vivo.

OBJECTIVES This study investigates using a machine learning (ML) model as a correlative measure of energy loss, a measure of TAA biomechanical function.

METHODS Biaxial tensile testing was performed on resected TAA tissue collected from patients undergoing surgery. The energy loss of the tissue was calculated and used as the representative output. Input parameters were collected from clinical assessments including observations from medical scans and genetic paneling. Four ML algorithms including Gaussian process regression were trained in Matlab.

RESULTS A total of 158 patients were considered (mean age 62 years, range 22-89 years, 78% male), including 11 healthy controls. The mean ascending aortic diameter was 47 $\pm$ 10 mm, with 46% having a bicuspid aortic valve. The best-performing model was found to give a greater correlative measure to energy loss ($R^2 = 0.63$) than the surprisingly poor performance of aortic diameter ($R^2 = 0.26$) and indexed aortic size ($R^2 = 0.32$). An echocardiogram-derived stiffness metric was investigated on a smaller subcohort of 67 patients as an additional input, improving the correlative performance from $R^2 = 0.46$ to $R^2 = 0.62$.

CONCLUSIONS A preliminary set of models demonstrated the ability of a ML algorithm to improve prediction of the mechanical function of TAA tissue. This model can use clinical data to provide additional information for risk stratification. (JACC Adv 2023;2:100637) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Department of Chemical Engineering, McGill University, Montreal, Quebec, Canada; [b]Division of Cardiac Surgery, McGill University Health Centre, Montreal, Quebec, Canada; [c]Division of Cardiology, McGill University Health Centre, Montreal, Quebec, Canada; [d]Division of Diagnostic Radiology, McGill University Health Centre, Montreal, Quebec, Canada; and the [e]Institut Universitaire de Cardiologie et de Pneumologie de Québec, Québec, Quebec, Canada.

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ABBREVIATIONS AND ACRONYMS

AscAo = ascending aorta

BAV = bicuspid aortic valve

BSA = body surface area

CCPM = cardiac cycle pressure modulus

GPR = Gaussian process regression

ML = machine learning

MSE = mean squared error

TAA = thoracic aortic aneurysm

TEE = transesophageal echocardiography

Thoracic aortic aneurysm (TAA) dissection and rupture occur acutely without clinical warning and are most often fatal. The causes of TAA are multiple and complex, including both degenerative and genetic factors.[1] Presently, the only treatment for those at risk of dissection or rupture of a TAA is prophylactic surgical intervention, for which the current surgical guidelines are based on aortic diameter with a threshold of 5.0 to 5.5 cm as the main decisional criterion.[2,3] Diameter is used as a crude estimate of the biomechanical state of the tissue.[4] Unfortunately, diameter is a poor predictor of risk, with approximately 40% of all ascending aortic dissections occurring below the diameter recommendation.[5] Dissection and rupture are localized mechanical failures of the aortic wall that occur when the stress exceeds the local mechanical integrity.[6] Aortic diameter is a poor marker of the biomechanical state of the tissue, and this critical uncertainty highlights the need for more robust metrics to stratify patients for surgery.

Degenerative processes in the medial layer of the aorta are associated with the occurrence of aortic dissections.[7] Analysis of ex vivo postmortem and surgical samples of aortic tissue has demonstrated that when the aorta undergoes pathologic remodeling (medial degeneration), the resultant biomechanical capabilities of the tissue are affected, causing the tissue to stiffen and lose structural function and integrity.[8-10] An accurate assessment of the biomechanical function of the aorta in vivo would help stratify patients for surgery.

Energy loss is a biomechanical metric that correlates with the extent of medial degeneration in the aortic tissue to a greater extent than aortic diameter.[11] More recent studies have also demonstrated energy loss correlations with multiple aortic wall failure criteria, including rupture strength and delamination strength,[10,12] distinguishing between patients with healthy, dilated, and dissected aortas, justifying the strong clinical capabilities of this parameter. In vivo interpretation has been attempted through transesophageal echocardiographic (TEE) imaging;[13] however, this method remains underdeveloped owing to the small cohort sizes and the variation of biomechanics with disease state, patient sex, age, and genetic variants.[14-16]

In recent years, there has been increased interest in machine learning (ML), a subset of artificial intelligence, for its promise for improving patient risk assessment.[17] Many different ML algorithms have been investigated for a wide range of applications in cardiovascular disease, including the prediction of complication risk and mortality.[18-20] ML is well placed to help move surgical guidelines beyond aneurysm size by leveraging data available in the clinic to "learn" to predict TAA biomechanical state prior to aortic resection. This would help identify the truly high-risk patients on either side of traditional size-based surgical intervention criteria.

Accordingly, this study seeks to leverage the added value of a ML approach to predict aortic biomechanical function based on an algorithm that can relate a wide range of patient-specific clinical data to aortic energy loss measured ex vivo. The training process of this model revealed the relative significance and covarying trends of various clinical factors with energy loss. Additionally, the added benefit of integrating an echocardiography-derived in vivo stiffness metric as an input factor, when available, was assessed for model improvement.

METHODS

STUDY COHORT. Informed consent was obtained from July 2012 to December 2021 from patients undergoing elective aortic valve or aortic resection surgery. Control aortic tissue was obtained from heart transplant donors and autopsy patients without heart or aortic disease.

A total of 158 patients were included in this study. Patient clinical information was collected during visits with a multidisciplinary aortopathy clinic at the McGill University Health Centre and retrospectively from patients' clinic notes and operation reports. All included variables are listed in **Table 1**. To eliminate inconsistencies between different imaging modalities, all aortic geometries were determined from TEE images performed at the time of surgery. Missing data was treated as described in Supplemental Table 1.

GENETIC PANELING. A total of 37 patients were recommended for genetic testing by the aortopathy clinic, via the Marfan's syndrome and Related Aortopathies Panel (Prevention Genetics) (Supplemental Table 2).

AORTIC GEOMETRIES. TEE images were performed after the administration of anesthetic but before the sternotomy using a GE Vivid 9 echocardiographic unit (GE Healthcare). The TEE probe was inserted into the esophagus to the level of the ascending aorta (AscAo), where an electrocardiogram (ECG)-gated, 2-dimensional long-axis view of the aortic valve and AscAo was captured, along with a 2-dimensional short-axis view at the point of maximum dilation. The largest diameter was measured at the sinus of Valsalva and the mid

AscAo from the long axis view using the linear measurement tool in InteleViewer (4-14-1-P249, Intelerad). Similarly, aortic surface area was measured from the short axis view using the elliptical/circular region of interest measurement tool. Both measurements were taken at the peak of the QRS complex of the ECG trace.

EX VIVO TENSILE ANALYSIS. Specimens were stored in physiologic saline at 4 °C until testing was completed, within 24 hours of tissue collection. The aortic ring was clipped for orientation upon collection, and 4 1.5 cm by 1.5 cm squares were sectioned, equally distributed around the circumference of the aorta. Five unique thickness measurements were taken for each testing square using a Mitutoyo Litematic VL-50A constant force digital micrometer (Mitutoyo Corp). The testing squares were then connected to a TA ElectroForce planar biaxial tensile tester (TA Instruments) using hooked 4 to 0 silk sutures in a 37 °C bath of Ringer's lactate solution. The testing squares were oriented for equiaxial stretching along their circumferential and longitudinal axes. Each sample was preconditioned for 8 cycles (ie, stretch and relaxation), followed by 4 cycles of data acquisition at a constant displacement rate of 0.1 mm/s in the range of 0% to 60% strain. The resultant stress-strain relations were analyzed using MATLAB (vR2021b MathWorks). A more detailed tensile methodology using this setup has been described previously.[11,21]

Energy loss of both axes was calculated from the engineering stress-strain relation. A mean value was taken from the 4 test squares. Energy loss is the percentage of elastic energy needed to stretch the testing square that is dissipated when the tissue is relaxed. The physiological interpretation is the percent of loss of elastic recoil energy in the tissue that is not returned to blood flow (maintaining normal Windkessel function).[22] The physical definition is the ratio of the area between the loading and unloading curve over the area under the loading curve (**Figure 1**).

TRANSESOPHAGEAL ECHOCARDIOGRAPHIC ANALYSIS. TEE analysis was performed on patients from February 2016 onward. When capturing the 2-dimensional short-axis view at the point of maximum dilation, an ECG-gated strain cycle was captured for 3 heartbeats. In tandem, an invasive arterial pressure trace was taken from the patient's radial artery for the same measurement interval.

TEE speckle-tracking strain analysis was performed using GE's EchoPAC software (GE Healthcare). This analysis has been described in more detail previously.[13] Using the strain definition provided by Voigt et al[23] for 2D speckle track echo ($\varepsilon = [\lambda - 1]$; $\lambda = L/L_0$), radial strain (ε_{Rad}) was converted to radial stretch (λ_{Rad}). The circumferential stretch (λ_{Circ}) profile was calculated using the conservation of volume: $\lambda_{Circ} = \sqrt{(1/\lambda_{Rad})}$. Cardiac cycle pressure modulus (CCPM), as defined in Emmott et al[13] was calculated as the slope of a linear interpolation of the radial blood pressure vs the circumferential wall stretch (**Figure 1**).

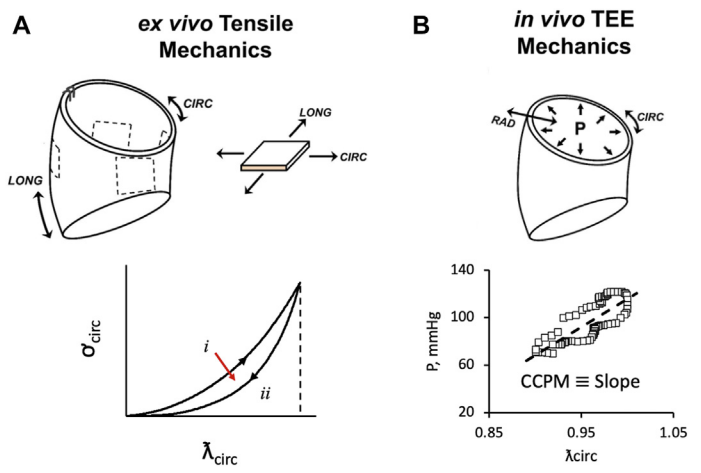
TABLE 1 Considered Clinical and Echocardiographic Variables

Input Variables	Variable Type	Input Options
Female	Logical	
Age (y)	Numeric	
Height (m)	Numeric	
BSA (m^2)	Numeric	
BMI (kg/m^2)	Numeric	
Systolic pressure (mm Hg)	Categorical	0 = 0-119, 1 = 120-129, 2 = 130-139, 3 = 140-179, 4 = >180
Diastolic pressure (mm Hg)	Categorical	0 = 0-79, 1 = 80-89, 2 = 90-119, 3 = >120
History of hypertension	Logical	
Diabetes (type I/II)	Logical	
Dyslipidemia	Logical	
Coronary artery disease	Logical	
Heavy weightlifting	Logical	
History of smoking	Logical	
Regular alcohol consumption	Logical	
NYHA heart failure symptoms	Logical	
Bicuspid aortic valve	Logical	
AscAo diameter (mm)	Logical	
SoV diameter (mm)	Numeric	
AscAo diameter/BSA (mm/m^2)	Numeric	
Type II aneurysm	Logical	
Family history	Logical	
Clinical featuring	Logical	
Marfan's syndrome	Categorical	0 = none, 1 = FBN1 VUS, 2 = Positive
Non-Marfan genetic variant	Logical	
VUS	Logical	
Aortic stenosis	Categorical	0 = none, 1 = mild, 2 = moderate, 3 = severe
Aortic regurgitation	Categorical	0 = none, 1 = mild, 2 = moderate, 3 = severe
CCPM (mm Hg)	Numeric	

AscAo = ascending aorta; BMI = body mass index; BSA = body surface area; CCPM = cardiac cycle pressure modulus; SoV = sinus of Valsalva; VUS = genetic variant of unknown significance.

MACHINE LEARNING ANALYSIS. Four ML models were trained, using the above-described clinical information as input variables and energy loss as the response variable. ML algorithms were performed using the MATLAB (vR2021b MathWorks) regression learner application from the Statistics and Machine Learning Toolbox. Patients were split randomly in a 75:25 ratio to create training and testing data sets (n = 119 and n = 39, respectively). Energy loss was capped at 2 standard deviations above the

FIGURE 1 Ascending Aorta Mechanics Using Ex Vivo Tensile Analysis and TEE-Derived Metric



(A) Four testing squares were taken around the circumference of the aortic ring. Specimens were stretched biaxially along the circumferential (circ) and longitudinal (long) axes to obtain the stress stretch profile. Energy loss is defined as the area between the loading and unloading curve divided by the area under the loading curve. Energy loss = Area(i)/[Area(i) + Area(ii)] × 100%. (B) In vivo, the aorta expands and recoils with changes in blood pressure. A transesophageal echocardiographic (TEE) speckle-track strain image of the radial (rad) strain was taken over 1 cardiac cycle and converted to circumferential (circ) stretch. Blood pressure-stretch curves were determined, with the slope of the linear fit being defined as the cardiac cycle pressure modulus (CCPM) (described by Emmott et al[13]).

population median, giving a maximum energy loss of 40%. Supervised learning was performed with 4 algorithms: linear regression, support vector machines, random forest, and Gaussian process regression (GPR). Model parameters are summarized in Supplemental Table 3. Performance was quantified in terms of the mean squared error (MSE) found by 5-fold cross-validation of the training data. Overfitting was assessed using the testing set through the change in MSE relative to the training data. An increase in MSE of <10% was acceptable.

Variable selection was conducted on the training data set (**Figure 2**). Initially, an F-score ranking method was used, a univariable selection method that determines the relationship each variable has to the output on an independent basis. The interactive importance of the variables was then determined through a wrapper method approach as a second round of variable selection.

A subcohort of 67 patients had sufficient TEE images to perform the TEE analysis, with some patients discarded due to poor visualization of the aortic walls. Supervised learning was performed using the same variable selection and ML algorithms as the full cohort. All 67 patients were used for model training, with validation done by 5-fold cross-validation.

STATISTICAL ANALYSIS. Statistical analyses were performed using GraphPad Prism, version 5.01 (GraphPad Software, Inc). Correlations were calculated using linear regression. The t-tests were performed using Welch's t-test for unequal variance. Prediction intervals and confidence intervals are shown on plots with dashed and dotted black lines, respectively. Results were considered significantly different when $P < 0.050$.

RESULTS

A total of 158 patients were recruited for the study, including 11 control patients (**Table 2**). The aneurysmal and control patients had mean ages of 63 ± 14 years and 49 ± 16 years ($P = 0.020$), respectively, and mean AscAo diameters of 49 ± 8 mm and 25 ± 5 mm ($P < 0.001$). Of the included patients, a subset of 67 underwent TEE strain imaging analysis. The TEE analysis cohort does not include control patients and had a similar mean age of 63 ± 14 years and diameter of 48 ± 9 mm to the full cohort.

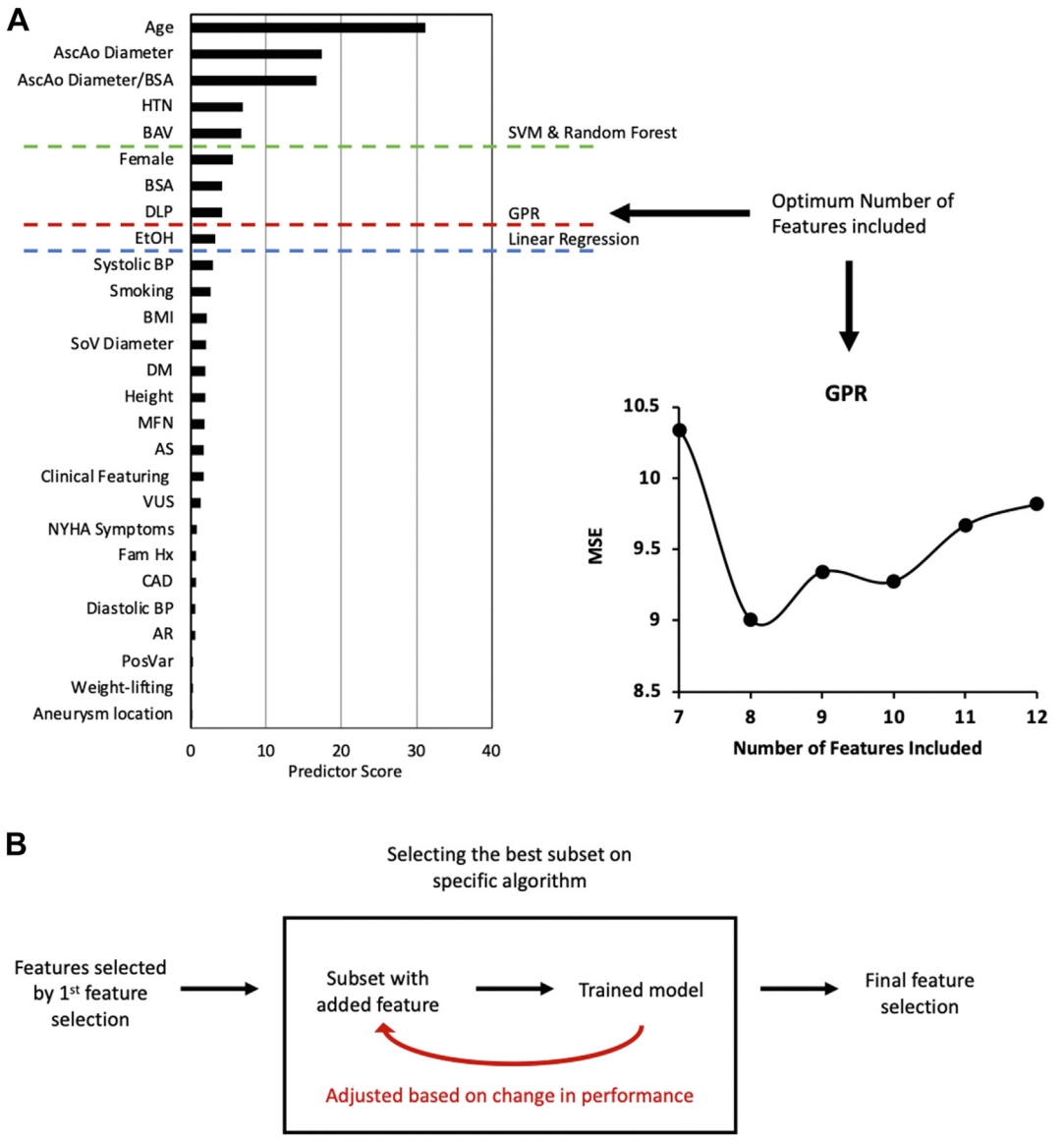
From the full cohort, the aneurysmal patients had a mean energy loss of 31% ± 5%, which was significantly greater than the mean energy loss for the healthy controls at 26% ± 3% ($P < 0.001$) (**Figure 3**), consistent with previous findings.[11] In this cohort, energy loss was found to correlate significantly with patient age ($r = 0.61$, $P < 0.001$), and with AscAo diameter ($r = 0.51$, $P < 0.001$).

Measured energy loss significantly increased with aortic diameter >55 mm, with the average energy loss in aortas <55 mm and >55 mm being 30% ± 5% and 34% ± 5%, respectively ($P < 0.001$). There was considerable variance in energy loss within these groups. Thus, at >55 mm, the surgical threshold, the measured energy loss values range from 21%, a normal value, to 39%, an extreme value.

PREDICTIVE MODEL FROM CLINICAL DATA. Variable selection was performed using f-test ranking for each of the 4 ML algorithms, followed by a wrapper-based feature selection as illustrated in **Figure 2**. Modeling performed via a GPR-based model was found to have the best performance compared to the other ML models and will be the focus going forward. Results from the remaining ML model types are provided in Supplemental Tables 5 and 6.

For the GPR-based model, a total of 13 variables were selected, including: age, AscAo diameter, AscAo diameter/body surface area (BSA), hypertension, bicuspid aortic valve (BAV), female, BSA,

FIGURE 2 Two-Stage Process for Selecting Significant Clinical Predictors



(A) An f-test was used to assign an importance score for each predictor with energy loss. Importance = −log (*P* value). The number of included variables for each model type was determined by MSE, exemplified with the GPR model type. Included variables for each model type are indicated with dotted lines. (B) A wrapper method used to consider the addition of the remaining features. A specific algorithm was retrained iteratively adjusting the subset of variables included to find an optimum based on minimum MSE. GPR = Gaussian process regression; MSE = mean squared error; SVM = support vector machine.

dyslipidemia, sinus of Valsalva diameter, type II aneurysm, aortic stenosis, Marfan syndrome, and heavy weightlifting. Final performance metrics are provided in Table 3.

The performance of currently considered diagnostic metrics for predicting energy loss was assessed. For a direct comparison with the ML models, linear regressions were created for each of these metrics using the training data set, and the same performance metrics were generated (Table 3). These models were found to be surprisingly poor for metrics including AscAo diameter (MSE = 17.5,

TABLE 2 Baseline Characteristics of Cohort

	Missing Data	Full Cohort (n = 158)[a]	TEE-Analysis Cohort (n = 67)
Basic patient information			
Age (y)	0	62 ± 14	63 ± 14
Female	0	22% (35)	22% (15)
Height (m)	<1%	1.7 ± 0.1	1.7 ± 0.1
BSA (m^2)	<1%	2.0 ± 0.2	2.0 ± 0.3
BMI (kg/m^2)	<1%	27 ± 5	27 ± 5
Disease specifications			
Ascending aortic diameter (mm)	0	47 ± 10	48 ± 9
Sinus of Valsalva diameter (mm)	7%	40 ± 9	40 ± 9
Aneurysm location	<1%		
AscAo		65% (103)	70% (47)
Sov		28% (44)	30% (20)
Nonaneurysmal		7% (11)	0% (0)
Bicuspid aortic valve	0	46% (73)	49% (33)
NYHA symptoms	11%	53% (84)	54% (36)
Aortic stenosis	0		
Mild		9% (15)	7% (5)
Mod		6% (9)	4% (3)
Severe		28% (45)	34% (23)
Aortic regurgitation	0		
Mild		22% (34)	22% (15)
Mod		22% (35)	24% (16)
Severe		17% (27)	18% (12)
Comorbidities			
History of hypertension	0	54% (85)	52% (35)
Diabetes (type I/II)	0	11% (18)	12% (8)
Dyslipidemia	0	26% (41)	24% (16)
Coronary artery disease	0	21% (33)	16% (11)
Life-style factors			
Heavy weightlifting	0	3% (5)	4% (3)
History of smoking	3%	16% (25)	7% (5)
Regular alcohol consumption	3%	14% (22)	22% (15)
Genetic information			
Family history	37%	26% (41)	24% (16)
Clinical featuring	0	7% (11)	9% (6)
Genetic testing done	0	25% (40)	36% (24)
Marfan's syndrome	0	3% (5)	3% (2)
Non-Marfan genetic variant	0	3% (5)	7% (5)
Variant of unknown significance	0	8% (12)	10% (7)

Values are mean ± SD or % (n). [a]Characteristics of training and testing datasets provided in Supplemental Table 4.

AscAo = ascending aorta; BMI = body mass index; BSA = body surface area; SoV = sinus of Valsalva; TEE = transesophageal echocardiographic.

R^2 = 0.26), AscAo diameter/BSA (MSE = 16.3, R^2 = 0.32), and AscAo surface area/height (MSE = 16.8, R^2 = 0.29). A multilinear regression of patient age and diameter was also considered to have a significant improvement (MSE = 11.4, R^2 = 0.51).

A performance plot of the resultant GPR-based model shows that 90% (107 of 119) of the predicted data points fall within a 95% prediction interval of the data (Figure 4). Most of the prediction outliers (6 of 12) occur at energy loss values >35%, with the predicted values being less than those that were measured. There is no significant difference in prediction error between the tricuspid aortic valve and BAV patients (tricuspid aortic valve MSE = 5.48, BAV MSE = 5.19, P = 0.852).

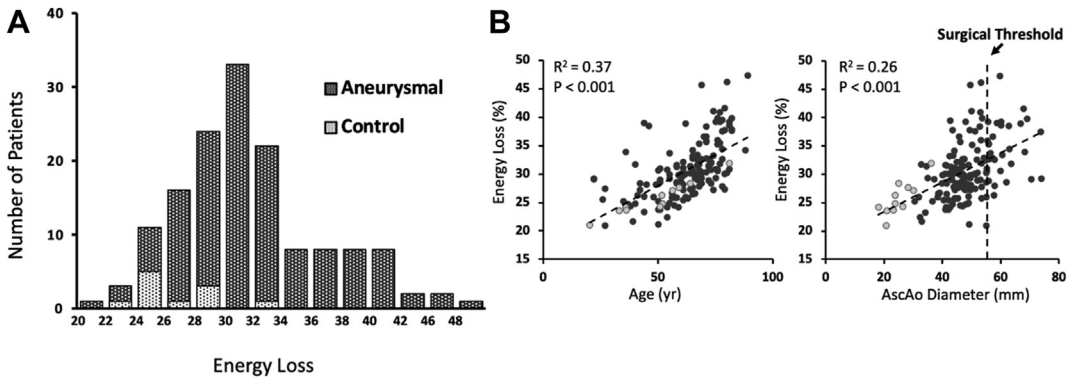
PREDICTIVE MODEL WITH TEE DERIVED STIFFNESS. To demonstrate model improvement with additional in vivo strain imaging data, a subcohort (n = 67) with an estimated CCPM modulus was added as an additional variable to the same variable selection determined in the previous section. The best-performing model for this data set was found again to be the GPR-based model (MSE = 8.60, R^2 = 0.62), noting that the performance of the original model using the full cohort (MSE = 8.69, R^2 = 0.63) was decreased (MSE = 12.0, R^2 = 0.46) with the significantly smaller TEE cohort. Once again, for a direct comparison with the models, a linear regression of CCPM was trained (MSE = 10.6, R^2 = 0.53). Performance plots for the linear regression of CCPM, the original GPR model, and combined GPR model with CCPM are shown in Figure 5.

DISCUSSION

A ML approach was used to predict the biomechanical function of human TAA tissue from patient-specific clinical data (Central Illustration). We have focused on energy loss as a measure of aortic tissue biomechanical function based on associations with medial degeneration and delamination strength.[10,11] Supervised learning techniques were used to computationally uncover relationships between the clinical data and energy loss. A regression-based ML model was found to have a much greater correlative measure with energy loss than simpler size-based metrics on their own (Table 3). Compared to the low correlation of AscAo diameter with energy loss (MSE = 17.5, R^2 = 0.26), a ML GPR-based model including 13 clinical variables has an improvement in MSE of up to 67% (MSE = 8.69, R^2 = 0.63) while justifying the added benefit of considering a broader range of patient information. In addition to age, genetic variants of the FBN1 gene and traditional cardiac risk factors such as hypertension were shown to have a positive influence on prediction. In a subgroup of subjects, prediction was further improved with the addition of a medical imaging-derived stiffness metric, CCPM, as an input variable.

IMPORTANCE OF AGE. The results of the f-test ranking of variable importance reveal that patient age, by far, has the strongest relationship to energy loss. Meaning the effect of the aorta's natural remodeling and stiffening with age is responsible for the largest amount of variation within this patient

FIGURE 3 Overview of Measured Energy Loss for Study Cohort



(A) Overlapping histogram of measured energy loss values for aneurysmal and control patients. (B) Scatter plots comparing ex vivo measured energy loss to common clinical metrics. (Left) Patient age at the time of surgery. (Right) In vivo measured ascending aortic diameter. Surgical diameter threshold indicated at 55 mm.

population. A recent study by Durbak et al[16] found similar evidence that age is the most influential factor in elastic energy storage in the thoracic aorta, with other studies finding similar relationships between age and mechanical testing indexes in both diseased[24] and healthy tissue.[25]

Energy loss predictions can be considered with respect to the population average for their age group. Levels of predicted risk can be assigned with respect to deviation from the population mean. This is exemplified by **Figure 6**, showing 2 groups of patients of similar age levels, indicated i-v. For example, patients iii and iv present as having degenerative aortopathy at 71 and 66 years old. Patient (#3) presents with a mildly dilated aorta of 46 mm, below the surgical cutoff; however, the energy loss is predicted at 36%, well above the population mean for this respective age level. By contrast, patient (#4) presents with similar diameter, age, and comorbidities but has a predicted energy loss much lower, at 30%. Here, the model demonstrates a capability to differentiate between patients having elevated biomechanical dysfunction. This can be particularly useful when considering patients in the diameter range of 4.5 to 5.5, especially now that recent guidelines are further reducing aortic diameter thresholds, exposing a larger population of patients to surgery.[26]

Old age is typically seen as a potential contradiction to surgery; however, here it is demonstrated that the biomechanical function of the aortic wall significantly worsens with old age, and as a result, the biomechanical burden associated with aneurysms can be much greater. This model provides a method of risk stratification that may assist in identifying older patients who may be at an elevated risk of aortic complications.

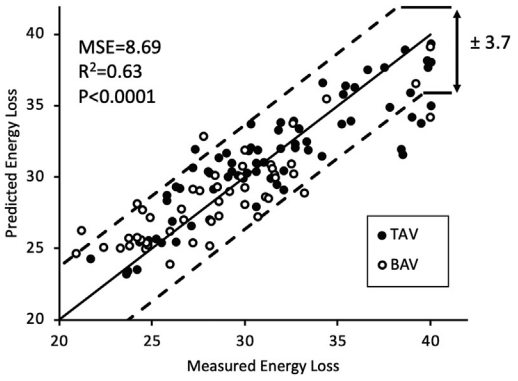
IMPORTANT CLINICAL PREDICTORS. It is important to note that variable selection in ML models represents factors that are correlative to the output but not necessarily causative. Many of the variables selected to be significant for this model are likely beneficial for their ability to establish the patient's phenotype as representative of the driving force for their disease. For example, comorbidities such as hypertension and dyslipidemia are associated with more acquired, degenerative forms of TAA. Different pathologies of aortopathy have differing mechanical characteristics, therefore being significant to this model. Guidelines currently rely principally on aortic diameter as the surgical guideline to determine timing of surgical intervention.[2] In this cohort, this relation was weak, confirming its known limitations in clinical care and implying a weak relationship between the biomechanical function of the tissue and its diameter.

TABLE 3 Summary of Model Performance With Full Cohort

Model Name	CV R^2	CV MSE	Testing MSE
Gaussian process regression model	0.63	8.69	8.78
AscAo diameter	0.26	17.5	15.7
AscAo diameter/BSA	0.32	16.3	13.5
AscAo surface area/height	0.29	16.8	15.9
Age, AscAo diameter	0.51	11.4	10.7

Characteristics of training and testing datasets provided in Supplemental Table 4.
AscAo = ascending aorta; BSA = body surface area; CV = cross validation; MSE = mean squared error.

FIGURE 4 Predictive Performance of GPR Model Trained on Full Cohort



Predicted values shown for training data set, with MSE and R^2 found by cross validation. Solid black line indicates line of perfect prediction at y = x. Dashed lines represent 95% prediction interval, with a width of 7.3% to 7.4%. BAV = bicuspid aortic valve, GPR = Gaussian process regression; TAV = tricuspid aortic valve.

Further, it was found to be less significant than patient age, despite a lack of acknowledgment of age in the current guidelines for treatment.

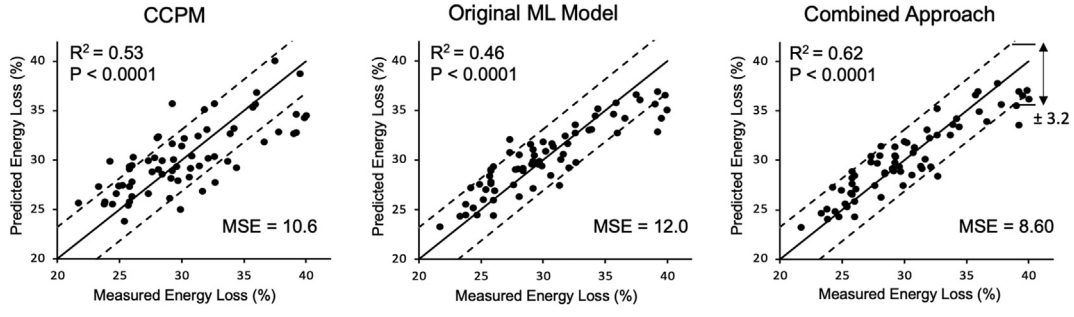
IMPORTANCE OF IN VIVO ESTIMATES. From the performance plot of the model (Figure 4), in the high energy loss region (>35%), it can be suggested that with extreme disease progression, mechanical function may be more heavily influenced by another driving force that is not being adequately represented by the considered factors. The lack of information on the growth rate of the aneurysm is potentially the missing piece in this problem. With the high rate of incidental findings in TAA patients, the rate of growth is unknown in most cases. Growth rate is known to be an important indicator of risk and has been speculated to correspond to different driving forces of medial degeneration.[14,27]

The integration of an in vivo estimate of biomechanical function (CCPM) into the model helps overcome the lack of real-time information. The metric CCPM, on its own, has the advantage of being directly related to the function of the aortic tissue at the time of surgery. However, the complexity of the image and lack of robustness of stiffness on its own make its correlative power to energy loss limited. The inclusion of CCPM in the ML model gives a greater prediction of energy loss than either individual method produces on its own.

FUTURE CONSIDERATIONS. The further development of this method would be clinically useful as a decision-support system. Particularly in low-resource centers, where a model of this type can be used as a screening tool for recommending patients to be considered more closely by a specialist. This approach can be easily integrated into the clinical environment as a desktop application in which patient data is inputted within the clinic or office, immediately generating biomechanical functional score.

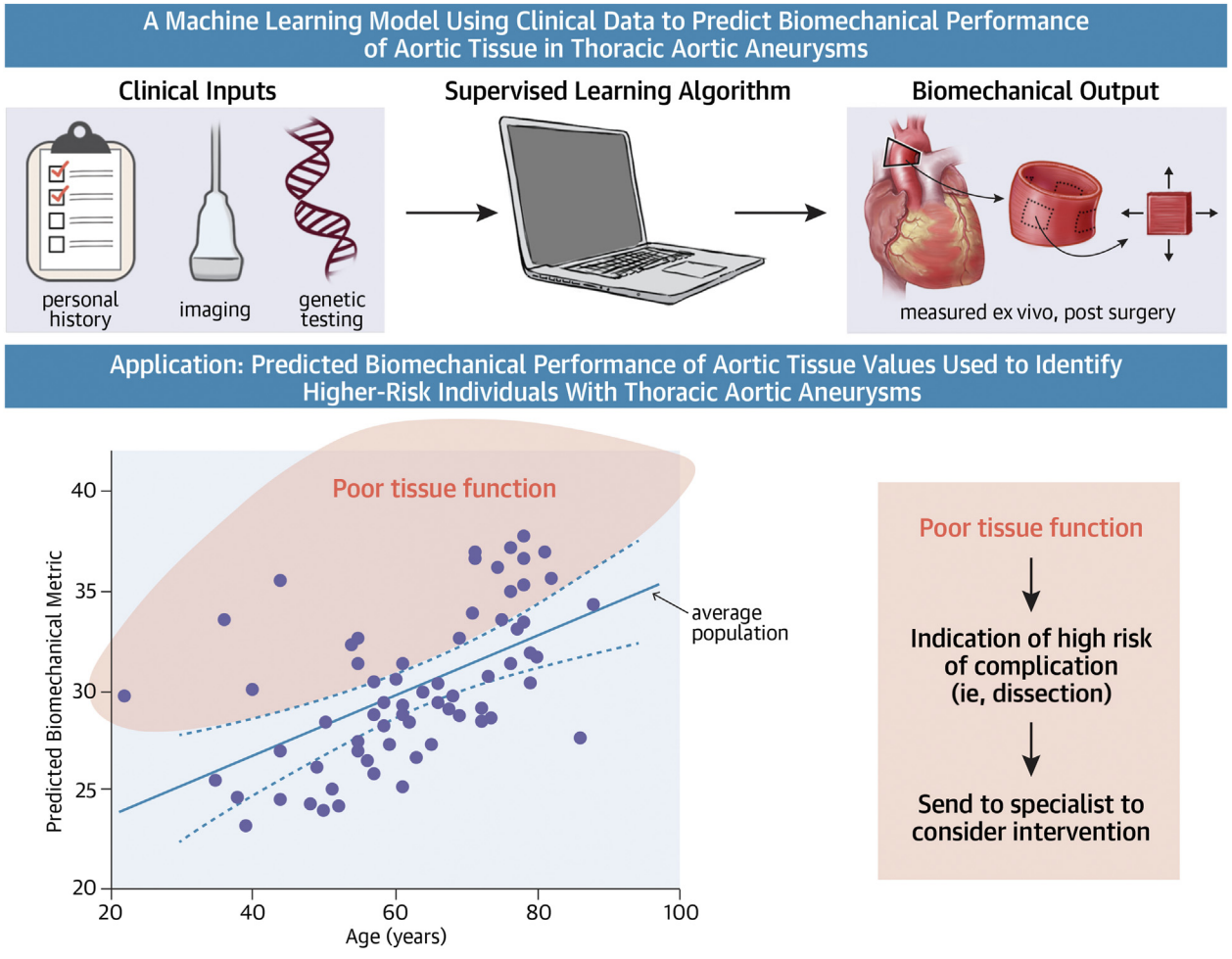
The relative success of this method, compared to the currently considered methods of diameter-based thresholds and echocardiographic-derived stiffness metrics, justifies the validity of this approach. The addition of more patients to the study cohort will help the model to "learn" and narrow the prediction intervals of the correlation.

FIGURE 5 Comparison of Prediction Performance of Considering Clinical Predictors and CCPM



Performance plots for (left) linear regression model trained on CCPM as only predictor, (middle) GPR model trained on 13 clinical predictors, and (right) GPR model trained on clinical predictors and CCPM. MSE and R^2 values based on cross validation. Solid black line indicating line of perfect prediction, 95% prediction interval shown with dashed line, having a width of 6.2% to 6.4%. CCPM = cardiac cycle pressure modulus; GPR = Gaussian process regression; MSE = mean squared error.

CENTRAL ILLUSTRATION **Machine Learning Approach to Thoracic Aortic Aneurysm Risk Management**



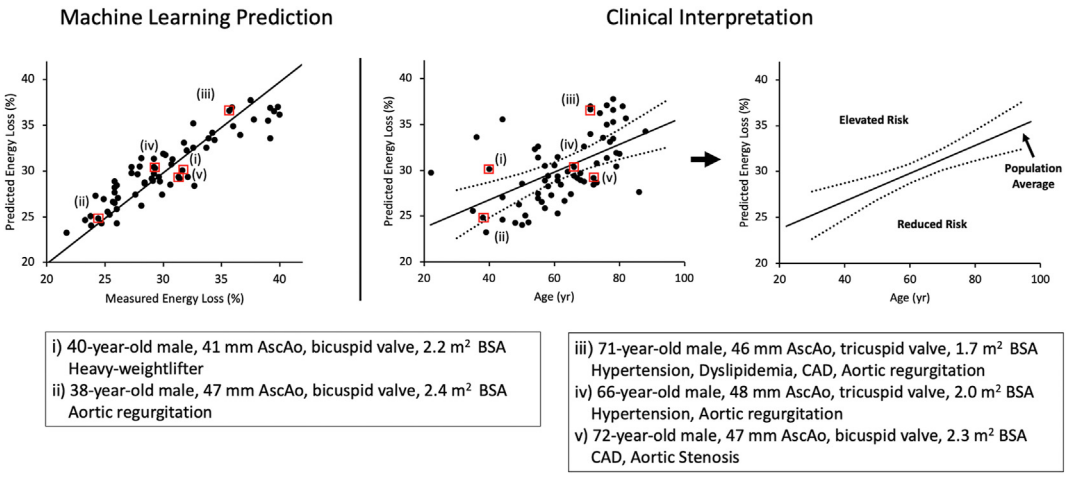
Kennedy L, et al. JACC Adv. 2023;2(8):100637.

A model for predicting the relative risk level of a patient was produced. Input data to the model included clinically accessible information such as past medical history, genetic paneling, and observations from echocardiographic images. A biomechanical metric measured by ex vivo tensile testing of the resected tissue was used as the output. Predicted biomechanical index was considered with reference to patient age to interpret relative risk. Some images were created using Biorender.

STUDY LIMITATIONS. Energy loss has been shown to be a robust mechanical property describing biomechanical states and is directly correlative of the pathological remodeling in the aortic wall.[11] However, the pathogenesis of dissection is multifactorial. Tissue material properties are not the sole factor at play.[6,7,28] Assessing the risk of dissection requires a multivariate approach. This work demonstrates that ML can be used to improve the prediction of aortic energy loss, a measurable property that we believe provides information on the integrity of the aortic wall. Meta-analysis of registries and ongoing clinical trials (IRAD and TITAN:SvS; NCT03536312) using the methods described in this paper could provide a more direct link to dissection and rupture given proper curation of the available data.

This approach is limited by the need for consistency within the data. For this reason, only TEE was used for geometric measurements, as every patient underwent imaging on the day of surgery. Size discrepancies between different imaging modalities, along with the further issue of inconsistencies in

FIGURE 6 Clinical Interpretation of Model Predictions by Indexing With Patient Age



i) 40-year-old male, 41 mm AscAo, bicuspid valve, 2.2 m² BSA
Heavy-weightlifter
ii) 38-year-old male, 47 mm AscAo, bicuspid valve, 2.4 m² BSA
Aortic regurgitation

iii) 71-year-old male, 46 mm AscAo, tricuspid valve, 1.7 m² BSA
Hypertension, Dyslipidemia, CAD, Aortic regurgitation
iv) 66-year-old male, 48 mm AscAo, tricuspid valve, 2.0 m² BSA
Hypertension, Aortic regurgitation
v) 72-year-old male, 47 mm AscAo, bicuspid valve, 2.3 m² BSA
CAD, Aortic Stenosis

(Left) Energy loss predictions are made using the Gaussian process regression model trained on TEE-analysis cohort with cardiac cycle pressure modulus included. (Right) Predicted energy loss values can be represented as a function of patient age at the time of surgery. Linear regression line represents population average, dotted line showing 99% confidence interval, providing potential risk categories while illustrating increased uncertainty of the model near the ends of the age range. Example patients (i) to (v) are indicated by red square. AscAo = ascending aorta; CAD = coronary artery disease; TEE = transesophageal echocardiography.

measuring techniques across centers present an obstacle when applying this to a clinical environment.

This study is also limited by the size of the patient cohort, causing heterogeneous groups, such as patients with BAV or genetic abnormalities, to be oversimplified. It should also be noted that socioeconomic data is not considered by this study, though it is becoming increasingly evident that economic class plays a significant role in a patient's likely risk factors.[29] Additionally, given the location of this study, the patient cohort is disproportionately made up of Caucasian patients. Therefore, these findings cannot be assumed to be applicable to all demographics.

CONCLUSIONS

This ML analysis demonstrates that an approach that integrates various clinical metrics provides a more accurate prediction of aortic mechanical function than the simpler size-based metrics currently employed. Preliminary models were able to incorporate common traditional cardiac risk factors such as comorbidities and Marfan's syndrome. Nevertheless, the limitations in prediction by this approach highlight the heterogeneous and complex nature of this disease. However, our results demonstrate that these limitations can be addressed at least in part with a combined approach using TEE speckle tracking-derived metrics as additional inputs to the model.

Overall, this study indicates the relative success of this method compared to those which are currently used. Our results provide strong support for the collection of mechanical data of this nature on a larger scale to further improve in vivo prediction of biomechanical function for clinical decision-making support.

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ADDRESS FOR CORRESPONDENCE: Dr Richard L. Leask, McGill University, 3610 University Street, Montreal, H4B 0CA Quebec, Canada. E-mail: richard.leask@mcgill.ca.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: Biomechanical indexes for TAA tissue can be better predicted by integrating a range of patient-specific data than with diameter-based metrics alone, with relevant additional metrics including patient age, sex, BSA, valve type, comorbidities, and genetic profile.

COMPETENCY IN MEDICAL KNOWLEDGE 2: The mechanical state of TAA tissue is dependent on patient age to a greater extent than disease progression and must be considered when interpreting data of this nature.

TRANSLATIONAL OUTLOOK 1: Although the cohort of this study is relatively small (n = 158), a larger-scale collection of biomechanical data on TAA tissue will lead to a better understanding of the relationships influencing patient risk and facilitate systems for better patient care.

TRANSLATIONAL OUTLOOK 2: An investigation is needed to compare the accuracy of risk levels assigned by an integrated ML approach compared to that of diameter thresholding by means of histopathological classification of tissue.

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APPENDIX For supplemental methods and tables and figures, please see the online version of this paper.