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Exploring the Association between Clinical Factors and Aortic Morphometry Using Neural Networks.

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ABSTRACT

Introduction: aortic morphometry varies across its segments and may reflect diverse clinical influences.

Objective: to identify which segments of the aorta show the greatest association with clinical variables using neural networks.

Materials and methods: an analytical and cross-sectional study was conducted with 801 adults from the Harvard Dataverse repository (2018–2019) who underwent non-contrast chest CT. Aortic diameters from the sinus of Valsalva to the abdominal aorta, measured using artificial intelligence, were assessed, along with 20 clinical variables. A multilayer neural network was applied as a nonlinear statistical analysis tool.

Results: in the performance analysis of the neural network model, the diameter with the lowest relative error was that of the middle descending aorta, whose relative error was 0.356 in the testing phase, obtaining a coefficient of determination of 0.613, indicating that the model explains 61.3% of the variability in diameter. Its most influential variables were age (importance of 0.168), creatinine (0.106), AST (0.082), and potassium (0.071). The mean square error was 0.324 in the training phase and 0.356 in the testing phase.

Conclusions: the neural network model reveals a stronger nonlinear association between clinical variables and the diameter of the mid-descending aorta, highlighting its sensitivity to hemodynamic and metabolic influences and reinforcing its value as a structural marker in cardiovascular disease assessment.

INTRODUCTION

The aorta is a complex vascular structure and the main blood vessel of the human body, in charge of carrying oxygenated blood from the left ventricle of the heart to organs and tissues.[1] Anatomically, it is divided into several segments: the ascending aorta, the aortic arch, the descending thoracic aorta and the abdominal aorta. Each of these segments presents particular structural characteristics and fulfills specific functions within systemic circulation.[2] Its morphometry varies over these segments owing to biomechanical, hemodynamic and ageing factors, which may reflect both physiological and pathological processes influenced by clinical, metabolic, liver, kidney and cardiovascular factors.[3,4] Although it is known that such factors affect vascular health in general, it is not clear which aortic segments present a stronger association with these clinical variables.

Understanding these relationships may provide useful information to characterize segmental vascular remodeling, and potentially contribute to the design of clinical strategies for individualized evaluation and monitoring. Particularly, learning which aortic segments display a greater sensitivity or correspondence with clinical data may help to prioritize diagnostic resources and to focus surveillance in areas more vulnerable to systemic changes.

In this regard, the goal of this investigation was identifying which segments of the aorta show a greater association with clinical variables using tomographic morphometric measurements. With this purpose, artificial neural network models were used, of the multilayer perceptron type, not with the goal of making a straight clinical prediction, but as an advanced statistical tool to explore complex and nonlinear association patterns between clinical variables and tomographic measurements of the aortic diameter. Through these methodologies, the degree of association between the different segments of the aorta and a common set of clinical variables are compared, with the aim of identifying what regions present a closer and more consistent relationship.

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This exploration may contribute novel evidence on the segmental differences in vascular response to clinical factors, and paves the way for new pathophysiological questions on the differential structural vulnerability of the aorta in different clinical scenarios.

MATERIALS AND METHODS

Design and population

Analytical and cross-sectional study on a secondary database, available at the Harvard Dataverse repository. This database included adults with and without comorbidities, who underwent non-contrast chest CT and an evaluation on arterial elasticity by an arteriosclerosis detector, between March 2018 and October 2019.

The population was made up by 801 adults of 18 years or older, all evaluated by chest CT. According to the authors of the original database, the participants did not present significant arterial alterations or diseases that may seriously compromise arterial structure. The following were ruled out: those with history of revascularization or aortic valve replacement, stent placement, genetic syndromes linked to aneurysms or aortic dissections (such as Marfan or Turner syndromes), relevant congenital anomalies of the aortic branches, inflammatory diseases with aortic compromise, acute arterial syndromes (as dissection or intramural hematoma), aortic aneurysms, conditions of hypovolemia or severe hemodynamic instability, advanced heart failure with reduced ejection fraction, and patients in hemodialysis. All available data in the repository were used, so no sampling or randomization techniques were applied.

Variables and measurements

Aortic diameters (quantitative values expressed in millimeters) were analyzed, following an anatomical order from proximal to distal: sinus of Valsalva, sinotubular junction, mid ascending aorta, proximal and mid portions of the aortic arch, proximal descending thoracic aorta, mid descending aorta, aorta at the level of the diaphragm and the abdominal portion in the celiac axis origin. According to the authors of the database, these diameters were obtained by an automated system based on AI, designed for organ segmentation from CT imaging.[5]

To model mid descending aorta diameter prediction, multiple independent variables were considered. These included demographic characteristics such as age (in years) and gender (0 = females, 1 = males); metabolic and biochemical parameters such as AST (U/L), creatinine (mg/dl), BMI (kg/m2), phosphorus (mg/dL), calcium (mg/dL), DBP and SBP (mmHg), triglycerides (mg/dL), ALT (U/L) and total cholesterol (mg/dL); as well as arterial stiffness index (M.CAVI, dimensionless). Also, clinical history was added, including chronic lung disease, osteoporosis, hypertension, diabetes mellitus and ischemic heart disease, all classified as present or absent. Finally, habits like smoking and alcohol consumption were considered, categorized as 0 for absence and 1 for presence. These variables were selected for their potential relevance on aortic diameter variation, considering both physiological and pathological aspects.

Statistical analysis

For the development of the prediction model for aortic segment diameter, a neural network of the multilayer perceptron (MLP) type was used. It is an automatic learning model made up of several layers of nodes or "neurons", where each neuron is connected to those of the following layer, allowing to capture nonlinear relationships between clinical variables and aortic diameters.[6] This type of neural network is capable of learning complex relationships between input and output variables, by a process of supervised training.[7] The network was trained with 544 cases (68.20%) and was validated with 254 cases (31.80%).

During the analysis of the neural network model performance, relative errors in the prediction of aortic segment diameters were evaluated, both in the training and in the testing phases. These relative errors, estimated as the percentage difference between the predicted values and the real values, allow to estimate the accuracy of the model, regardless of the data scale.

Next, we carried out an independent analysis of the mid descending aorta segment, because of its better performance in prediction. In this analysis, we observed the nonlinear relationships between variables and mid descending aorta diameter. The estimated coefficients in the hidden layers reflected how each covariate influences on intermediary activations, which are combined to generate the final prediction. The covariate relationships with the mid descending aorta diameters were evaluated in terms of relative significance of each one, which enabled the identification of the most influential factors in aortic morphology.

Data analysis and processing, including using the neural network of the multilayer perceptron type, was made by the SPSS 25TM software.

Ethical considerations

The database used in this study comes from the open access repository of the Harvard Dataverse, which is available under the Creative Commons Zero (CC0) license, which enables its free use. As we worked with secondary data that were already anonymous, it was not necessary to obtain additional specific ethical permits or authorizations. Likewise, participant data confidentiality was ensured, by following the principles established in the Declaration of Helsinki.

The database is available at the following link:
https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/C0YY9I

The database specifications are available at the following link:
https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/C0YY9I

RESULTS

In the descriptive analysis, the participants presented a wide clinical and biological variability. The average age was 57.97 years, with a range from 18 to 95. High levels of dispersion were observed in BMI, blood pressure, biomarkers (AST, ALT, creatinine and M.CAVI), cholesterol and triglycerides (63.5%) or osteoporosis (83.1%). Only 3.6% reported chronic lung disease. This heterogeneity is key for the clinical associations evaluated *(Table 1).*

A prediction model was developed by a neural network of the multilayer perceptron type, using 798 valid cases, of whom 68.2% was devoted to training and 31.8% to testing. The network added 20 standardized covariates in the input layer, related to demographic, clinical and biochemical factors. The architecture included a hidden layer with 12 nodes and hyperbolic tangent activation function. The output layer comprised 9 nodes, corresponding to analyzed aortic segments. The dependent variables were standardized and

TABLE 1.
Descriptive statistics and frequency of clinical variables

Descriptive statistics				
Variable (unit)	**Minimum**	**Maximum**	**Mean**	**Standard deviation**
Age (years)	18	95	57.97	14.14
BMI (kg/m²)	15.3	40.2	24.55	33.01
SBP (mmHg)	91	223	148.48	20.45
DBP (mmHg)	52	118	79.37	10.28
M.CAVI (arterial stiffness index)	3.215	14.735	818.83	1.42
ALT (U/L)	1	599	27.6	305.21
AST (U/L)	10	444	24.57	21.01
Creatinine (mg/dL)	0.05	6.25	0.8535	0.31499
Calcium (mg/dL)	7.21	234.47	92.22	798.34
Phosphorus (mg/dL)	1.3	7.16	31.9	0.56489
Total cholesterol (mg/dL)	72.97	375.29	1719.27	4322.52
Triglycerides (mg/dL)	36.28	1908.85	1662.69	16873.85
Aortic sinus of Valsalva (mm)	21.4	51.1	35.23	42.53
Sinotubular junction (mm)	23	51.8	32.98	40.45
Mid ascending aorta (mm)	23.5	53.6	37.12	47.31
Proximal aortic arch (mm)	22	44.7	33.15	37.08
Mid aortic arch (mm)	19.3	39.4	30.31	30.83
Descending thoracic aorta (mm)	19.5	40.6	28.6	32.77
Mid descending aorta (mm)	15.9	35.5	25.64	31.94
Aorta in the diaphragm (mm)	15.3	33.5	25.25	25.95
Abdominal aorta(mm)	13	31.7	23.85	25.63
Frequencies				
Variable	**Category**	**Frequency**	**Porcentaje**	
Smoker	No	536	66,9%	
	Yes	265	33,1%	
Alcohol consumption	No	574	71,7%	
	Yes	227	28,3%	
DM (Diabetes Mellitus)	No	509	63,5%	
	Type 1	115	14,4%	
	Type 2	177	22,1%	
Osteoporosis	No	666	83,1%	
	Yes	135	16,9%	
Chronic lung disease	No	772	96,4%	
	Yes	29	3,6%	

TABLE 2.
Summary of case processing and architecture of the neural network model for the prediction of aortic segment diameters

Category	Element	Detail
Case processing	Total of valid cases	798 (100%)
	Cases used for training	544 (68.2%)
	Cases used for testing	254 (31.8%)
	Ruled out cases	3
Neural network model	Type of network	Multilayer perceptron
	Input layer	
	Number of covariates	20
	Variables included	Gender, age, BMI, SBP, DBP, M.CAVI, ALT, AST, smoking, alcohol, HTN, DM, CAD, osteoporosis, chronic lung disease, creatinine, calcium, phosphorus, total cholesterol, triglycerides
	Covariate scaling	Standardized
	Hidden layer	
	Number of hidden layers	1
	Units in the hidden layer	12
	Activation function	Hyperbolic tangent
	Output layer	
	Dependent variables	Aortic sinus of Valsalva, sinotubular junction, mid ascending aorta, proximal aortic arch, mid aortic arch, descending thoracic aorta, mid descending aorta, aorta in the diaphragm, abdominal aorta
	Number of units	9
	Dependent variables scaling	Standardized
	Activation function	Identity
	Error function	Sum of squared errors

the linear activation function was applied with an error criterion based on the sum of squared errors *(Table 2)*.

The analysis of relative errors showed that the model represented the relationship between clinical variables and the mid descending aorta diameter with more accuracy, both in the training phase (0.383) and in the testing phase (0.356). In contrast, the greatest inaccuracies were observed in the aortic sinus of Valsalva and the sinotubular junction. These results indicate a better capacity of the model to capture the relationship in the descending aorta segments *(Table 3)*.

As the neural network showed a higher accuracy in the estimation of the mid descending aorta diameter, a specific analysis was made on this segment. The hidden layers of the model capture nonlinear relationships between clinical covariates and the aortic diameters. In this analysis, the intermediary units of the hidden layers (H(1:1) to H(1:8)) show how the input variables affect the final prediction. The coefficients of the hidden layers indicate that an increase in age is associated to an increase in the mid descending aorta diameter, with significant values of 0.576 in H(1:1) and 0.638 in H(1:8). In contrast, gender shows a more variable relationship, with both negative and positive coefficients, reflecting its varying influence on the processing stages. In brief, the results show how the neural network models the

TABLE 3.
Relative errors in the prediction of aortic diameters by phase of the multilayer perceptron model (training and testing)

Phase	Dependent variable	Relative error
Training	Aortic sinus of Valsalva	0.714
	Sinotubular junction	0.703
	Mid ascending aorta	0.532
	Proximal aortic arch	0.514
	Mid aortic arch	0.531
	Descending thoracic aorta	0.551
	Mid descending aorta	0.383
	Aorta in the diaphragm	0.544
	Abdominal aorta	0.573
Testing	Aortic sinus of Valsalva	0.798
	Sinotubular junction	0.716
	Mid ascending aorta	0.521
	Proximal aortic arch	0.584
	Mid aortic arch	0.630
	Descending thoracic aorta	0.596
	Mid descending aorta	0.356
	Aorta in the diaphragm	0.515
	Abdominal aorta	0.587
	Función de error	Suma de cuadrados

complex nonlinear relationships between clinical variables and the aortic morphology, with special emphasis on the mid descending aorta *(Table 4).*

The analysis of the importance of the variables for the mid descending aorta diameter revealed that age was the most influential one (0.168, 100%). Other significant variables were AST (0.092, 54.7%), creatinine (0.084, 49.9%), BMI (0.068, 40.2%) and phosphorus (0.063, 37.5%). Metabolic kidney health factors showed a significant relationship with aortic diameter. Variables such as DBP (0.059, 35.2%) and triglycerides (0.057, 33.8%) were also relevant, just as ALT (0.055, 32.8%). With less impact, there were M.CAVI (0.043, 25.5%) and chronic lung disease (0.040, 24.0%). The variables with less relevance were osteoporosis, smoking, HTN, alcohol consumption, DM and CAD. In summary, age and renal health presented a higher influence on aortic diameter, while the other conditions had a lesser impact *(Table 5).*

The dispersion graph between the values observed and predicted for the mid descending aorta diameter shows a moderate relationship, with an R2 determination coefficient of 0.613. In the graph, the observed values are represented in the X axis, and the predicted values in the Y axis. Most points are grouped close to the identity line, indicating that the multilayer perceptron model captures a significant part of variability in aortic diameters. However, the dispersion of some points reflects deviations and an error margin in predictions. This pattern suggests that the model explains 61.3% of diameter variability, but still presents an error margin of 38.7%, indicating the need to optimize the model accuracy in future analysis *(Figure 1).*

DISCUSSION

The results obtained in this study show that the clinical variables, such as blood pressure, calcium and phosphorus levels, and the presence of dyslipidemia had a significant association with the mid descending aorta diameter; while this relationship was not observed with the same strength in other aortic segments. This finding is particularly relevant, as it suggests that the clinical behavior of certain systemic conditions (such as hypertension and metabolic alterations) may have a specific impact on this portion of the aorta, and not necessarily on the proximal or distal segments with the same intensity.

The mid descending aorta is in a transition area between the ascending aorta, which has a more elastic structure, and less exposed to direct systolic pressure, and the abdominal aorta, which has a stiffer behavior.[8,9] This location may ex-

TABLE 4.
Estimation of parameters in the regression model for the prediction of mid descending aorta diameter

Predictor	(H(1:1))	1(H(1:2))	1(H(1:3))	1(H(1:4))	1(H(1:5))	(H(1:6))	(H(1:7))	(H(1:8))	Mid descending aorta
Bias	-0.325	-0.411	-0.160	-0.167	-0.119	0.190	0.409	0.483	-0.058
Gender	-0.289	-0.156	0.179	0.501	0.058	0.151	-0.266	-0.266	-0.266
Age	0.576	-0.274	0.075	-0.065	-0.200	0.419	-0.232	0.638	0.638
BMI	0.269	-0.144	0.331	-0.040	0.180	0.045	0.183	-0.036	-0.036
SBP	0.457	0.157	0.045	0.409	-0.281	-0.283	0.209	0.104	0.104
DBP	-0.291	-0.325	-0.263	-0.518	0.149	-0.189	-0.511	0.578	0.578
M.CAVI	-0.195	0.292	0.556	0.035	-0.520	0.226	0.422	0.129	0.129
ALT	-0.573	-0.009	0.120	-0.305	-0.234	-0.207	-0.476	-0.052	-0.052
AST	0.230	0.463	0.204	-0.028	-0.118	0.251	-0.092	0.047	0.047
Smoking	0.419	0.075	-0.420	-0.299	-0.395	-0.430	-0.293	-0.262	-0.262
Alcohol	-0.223	-0.260	0.363	-0.334	0.233	-0.480	0.016	0.108	0.108
HTN	-0.136	0.049	0.332	0.157	-0.470	-0.024	0.060	0.190	0.190
DM	0.103	-0.245	0.196	0.349	-0.015	0.370	-0.215	0.009	0.009
CAD	-0.001	0.128	-0.117	-0.456	0.104	-0.283	-0.504	0.146	0.146
Osteoporosis	-0.462	-0.370	0.235	-0.164	-0.284	-0.027	-0.088	0.121	0.121
Chronic lung disease	0.483	0.515	0.186	-0.276	-0.003	0.406	0.284	-0.282	-0.282
Creatinine	0.325	-0.420	0.051	0.048	-0.354	-0.164	0.165	-0.007	-0.007
Calcium	0.292	0.438	0.033	0.319	0.151	-0.056	0.058	-0.099	-0.099
Phosphorus	-0.224	0.343	-0.377	0.366	0.027	0.025	0.072	0.359	0.359
Total cholesterol	-0.164	-0.245	0.276	0.264	0.096	0.236	0.018	-0.238	-0.238
Triglycerides	0.360	-0.431	-0.089	0.421	0.185	-0.468	-0.374	-0.176	-0.176

plain why this segment is more susceptible to hemodynamic and metabolic alterations. An elevated systolic BP and changes in elasticity of the aorta can be more evident in the mid descending aorta, as this segment receives the heart pulsation forces directly, but could be more affected by the vascular tone modifications caused by comorbidities, such as hypertension and dyslipidemia.[9]

The mid descending aorta is a critical site for the manifestation of dysfunctions in arterial elasticity due to the aortic stiffness associated with chronic hypertension and an imbalance in the lipid and mineral metabolism.[10] Dyslipidemia can promote the formation of atherosclerotic plaques in this segment, and an increase in the calcium levels in blood may induce aortic calcification, processes that may affect more intensely the mid descending aorta.[9,11,12] These metabolic factors, along with stiffness induced by hypertension, may contribute to the loss of distensibility in this part of the aorta, which makes it more vulnerable to structural and functional alterations.

Furthermore, the metabolic factors such as elevated calcium and phosphorus levels, as in the case of patients with chronic kidney disease, may affect the composition of the aortic wall; particularly in the region of the mid descending aorta, favoring calcification and endothelial dysfunction.[13]

TABLE 5.
Significance of independent variables in the prediction of mid descending aorta diameter

Variable	Significance	Normalized significance
Age	0.168	100%
AST	0.092	54.7%
Creatinine	0.084	49.9%
BMI	0.068	40.2%
Phosphorus	0.063	37.5%
Calcium	0.061	36.1%
DBP	0.059	35.2%
Triglycerides	0.057	33.8%
ALT	0.055	32.8%
SBP	0.053	31.7%
Total cholesterol	0.050	29.5%
M.CAVI	0.043	25.5%
Chronic lung disease	0.040	24.0%
Gender	0.035	20.7%
Osteoporosis	0.018	10.7%
Smoking	0.013	7.4%
HTN	0.013	8.0%
Alcohol consumption	0.010	5.9%
DM	0.010	5.9%
CAD	0.008	5.0%

This would explain why this segment shows a greater association with the clinical variables observed, in comparison with other more proximal or distal segments of the aorta, that may be less sensitive to these factors.

The dispersion graph between the observed and estimated values of the mid descending aorta diameter, generated by a multilayer perceptron model, showed a moderate relationship, with an R2 determination coefficient of 0.613, indicating that the model explains approximately 61.3% of aortic diameter variability. This moderate performance could be attributed to multiple physiological, clinical and methodological factors, as aortic morphology is the result of complex processes such as vascular ageing, arterial remodeling, aortic wall stiffness, oxidative stress and chronic inflammation, which are mediated by genetic, metabolic and hemodynamic components, that are not always reflected in routine clinical variables.[14,15]

This result has significant clinical implications, as the mid descending aorta could be a sensitive marker of vascular alterations in individuals with metabolic and cardiovascular diseases, particularly in those with uncontrolled hypertension or dyslipidemia. Physicians may focus on this aortic segment as a priority target to monitor structural changes in patients in high risk, as in those with established cardiovascular disease or those in risk of aortic aneurysms. In this regard, this finding also contributes to the anatomical and physiological understanding of the mid descending aorta, by highlighting its role as a vascular area susceptible to hemodynamic and metabolic influences, reinforcing its relevance as a structural marker in the study of cardiovascular diseases.

In this scenario, physicians can use the identified clinical variables, such as blood pressure, calcium and phosphorus levels, and dyslipidemia to estimate the risk of aortic alterations in this segment, which enables making more informed decisions on additional tests or preventive interventions.

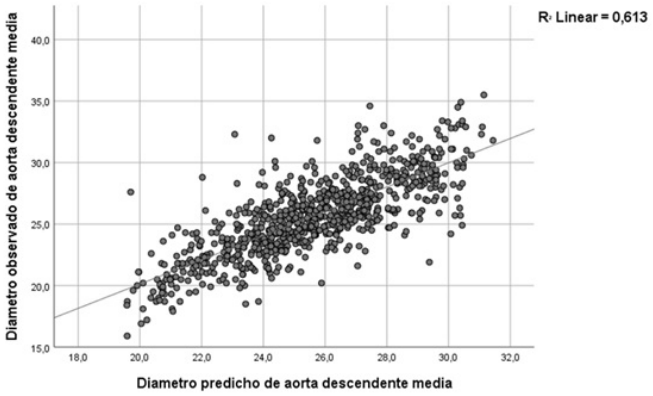

FIGURE 1.
Dispersion graph with coefficient of determination between values observed for the mid descending aorta diameter, obtained by non-contrast CT and predicted values for the mid descending aorta obtained by multilayer perceptron

Moreover, the developed model could be implemented as a clinical support tool for an early identification of patients in risk of aortic diseases, optimizing care and reducing the need for invasive testing in its initial stages, which favors a more efficient and customized care.

The main limitations of this study include a cross-sectional design, which does not enable establishing causal relationships; and the lack of longitudinal follow-up, which prevents observing the course of aortic diameter over time. Furthermore, the study does not consider confounding factors such as genetics or lifestyle, and the evaluation of aortic diameter by CT mediated by AI could present technical biases. Finally, the sample may not be representative for the general population, limiting the generalization of results.

To conclude, the results of the multilayer neural network suggest that clinical variables and cardiovascular risk factors present a nonlinear association with the diameter of the mid descending aorta. This association becomes evident in the adequate predictive capacity of the model for said segment (lower relative error in both phases of the model), as well as in the influence observed of these variables on the activations of the hidden layers and the output layer. Likewise, although this is not a causal or inferential analysis, the results reinforce the usefulness of neural networks to model complex clinical relationships affecting aortic morphology. It is advised to reproduce this research in more extensive cohorts.

We suggest performing longitudinal studies that would enable evaluating aortic diameter changes over time and establishing causal relationships. Likewise, we recommend, for future studies, to include genetic and lifestyle variables, besides validating automated measurements with manual methods. Finally, extending the sample to more diverse populations would improve the generalization of the findings.

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