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Voice Signal Characteristics Are Independently Associated With Coronary Artery Disease

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Abstract

Objective: Voice signal analysis is an emerging noninvasive diagnostic tool. The current study tested the hypothesis that patient voice signal characteristics are associated with the presence of coronary artery disease (CAD).

Methods: The study population included 138 patients who were enrolled between January 1, 2015, and February 28, 2017: 37 control subjects and 101 subjects who underwent planned coronary angiogram. All subjects had their voice signal recorded to their smartphone 3 times: reading a text, describing a positive emotional experience, and describing a negative emotional experience. The Mel Frequency Cepstral Coefficients were used to extract prespecified voice features from all 3 recordings. Voice was recorded before the angiogram and analysis was blinded with respect to patient data.

Results: Final study cohort included 101 patients, of whom 71 (71%) had CAD. Compared with subjects without CAD, patients with CAD were older (median, 63 years; interquartile range [IQR], 55-68 years vs median, 53 years; IQR, 42-66 years; P=.003) and had a higher 10-year atherosclerotic cardiovascular disease (ASCVD) risk score (9.4%; IQR, 5.0-18.7 vs 2.7%; IQR, 1.6-11.8; P=.005). Univariate binary logistic regression analysis identified 5 voice features that were associated with CAD (P<.05 for all). Multivariate binary logistic regression with adjustment for ASCVD risk score identified 2 voice features that were independently associated with CAD (odds ratio [OR], 0.37; 95% CI, 0.18-0.79; and 4.01; 95% CI, 1.25-12.84; P=.009 and P=.02, respectively). Both features were more strongly associated with CAD when patients were asked to describe an emotionally significant experience.

Conclusion: This study suggests a potential relationship between voice characteristics and CAD, with clinical implications for telemedicine—when clinical health care is provided at a distance.

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Coronary artery disease (CAD) is an important public health problem in industrialized and developing nations alike, and a leading cause of cardiovascular mortality worldwide. All current guidelines on the prevention of CAD in clinical practice recommend assessment of total cardiovascular risk, because atherosclerosis is usually the product of a number of risk factors. Traditional cardiovascular risk factors such as age, sex, blood pressure, smoking status, cholesterol (total, low-density lipoprotein, and high-density lipoprotein), and diabetes mellitus have been used for estimating pretest probability of existing CAD using tools such as the Framingham risk score, the American College of Cardiology (ACC)/American Heart Association (AHA) atherosclerotic cardiovascular disease (ASCVD) Risk Equation, and the European Systematic COronary Risk Evaluation (SCORE) model.[1-3] However, multiple studies have demonstrated the limited utility of such scores in particular cohorts of patients, such as sedentary subjects with central obesity, asymptomatic subjects with preclinical evidence of atherosclerosis, subjects with chronic kidney disease, and patients with inflammatory disorders.[2] Emerging nontraditional risk factors, such as inflammatory biomarkers, computed tomography calcium score, and endothelial dysfunction, have already been shown to improve available models.[4-7] However, there is still a need for simple noninvasive tests to facilitate screening and improve the accuracy of the cardiovascular risk estimation models by incorporating additional markers of cardiovascular disease.

Voice signal characteristics have been suggested to be associated with a number of

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different pathological entities including dyslexia, attention deficit/hyperactivity disorder, Parkinson disease, and other neurological disorders.[8-10] In a study that evaluated voice characteristics among children with autism spectrum disorder, the authors were able to use pitch variability in classifying autism spectrum disorder among the study population with an accuracy of 80%.[9] Preliminary observations of voice samples from healthy subjects and patients with heart disease suggested possible distinct voice features in patients with heart disease.[8] However, there is currently no data on the association between CAD and voice characteristics. As a systemic inflammatory process, atherosclerosis is associated with multiple pathologic processes such as chronic kidney disease, cerebrovascular disease, vascular dementia, retinopathy, and peripheral artery disease.[11] We hypothesize that this process might also involve anatomic structures associated with voice production.

Therefore, the purpose of the current hypothesis-generating study was to identify the association between voice characteristics and CAD among patients referred for coronary angiogram.

METHODS

Study Population

The study population included a total of 166 patients who were enrolled between January 1, 2015, and February 28, 2017, including 129 patients who presented for coronary angiography, 22 apparently healthy control volunteers, and 15 control subjects who were referred to noncardiac procedures (including hernia operations, varicose vein procedures, and dermatologic and ophthalmologic procedures). We enrolled patients who were referred to the chest pain clinic and were not known to have preexisting CAD. All subjects underwent coronary angiogram between February 1, 2014, and May 31, 2016 in Mayo Clinic, Rochester, Minnesota. The 2 inclusion criteria for the current study were the possession of smartphone and scheduled elective coronary angiogram for suspected CAD. Exclusion criteria included known history of CAD or previous coronary intervention, current or known history of voice disorder either primary or secondary to neuromuscular or other pathology, age less than 18 years, and pregnancy. Study protocol was approved by the institutional review board (#IRB 14-000058), and all patients provided informed consent for participation. The purpose of control groups was to improve overall quality of voice features normalization, and to exclude the possibility of bias associated with preprocedural anxiety. The first control group (N=22) consisted of healthy volunteers who did not undergo any procedure but followed the same study protocol, and the second control group (N=15) consisted of Mayo Clinic patients free of known CAD who underwent noncardiac procedures. For the first control group, subjects were recruited among Mayo employees and community members using various advertisement methods, including the Rochester Mayo Clinic Classified System and flyers.

Voice Characteristics

Following enrollment and before the planned coronary angiogram, each patient was asked to speak aloud a predetermined amount of text into a recording device. Recording was performed by the patients with no prior coaching or training. Voice was recorded, stored online, and analyzed for multiple features of voice intensity and frequency using "Beyond Verbal Communications" clinical trial application, which was downloaded to the patients' personal smartphone.[8] The application was available for any type of smartphone. Analysis was blinded with respect to patient data. The voice analysis in this study was done in a semiautomated fashion. To maintain high-level quality recordings, all the voice files were examined by a voice analytics expert. Then, a defined set of acoustic features was extracted from each good quality voice file. Thus, no editing or subjective interpretation was required in the process. A total of three 30-second separate baseline voice recordings were documented and analyzed for each participant: R1—participant was asked to read a prespecified text; R2—participant was asked to describe a positive emotional experience; and R3—patient was asked to describe a negative emotional experience. The Mel Frequency Cepstral Coefficients (MFCCs) were used to extract information from the voice signal.[12] The MFCC feature extraction is a sound processing tool that is used for voice

TABLE 1. Characteristic of Study Population[a,b]

Characteristic	All (N=101)	CAD—Yes (N=71)	CAD—No (N=30)	*P*
Age (y)	61 (51-67)	63 (55-68)	53 (42-66)	.003
Sex: male	54 (54)	40 (56)	14 (47)	.37
SBP (mm Hg)	123 (114-139)	126 (114-139)	120 (111-133)	.43
DBP (mm Hg)	72 (64-79)	73 (64-80)	71 (63-76)	.62
BMI (kg/m^2)	30 (27-34)	30 (27-34)	31 (26-37)	.20
Treated hypertension	45 (45)	38 (54)	7 (23)	.005
Treated hyperlipidemia	41 (41)	34 (48)	7 (23)	.02
Diabetes mellitus	15 (15)	14 (20)	1 (3)	.03
Active smoking	13 (13)	9 (13)	4 (13)	.60
Sleep apnea	26 (26)	18 (25)	8 (27)	.54
Family history of CAD	74 (73)	50 (70)	24 (80)	.24
CKD	37 (37)	31 (44)	6 (20)	.02
PVD	2 (2)	2 (3)	0	>.99
History of TIA	1(1)	1(1)	0	>.99
History of CVA	2 (2)	2 (3)	0	>.99
ACS presentation	8 ()	6 (8)	2 (7)	.53
Creatinine (mg/dL)	0.9 (0.8-1.1)	0.9 (0.8-1.1)	0.9 (0.8-1.1)	.15
Hemoglobin (g/dL)	13.8 (12.7-14.9)	13.9 (12.7-14.8)	13.6 (12.8-14.9)	.77
Total cholesterol (mg/dL)	180 (156-207)	179 (149-205)	188 (162-212)	.28
Triglycerides (mg/dL)	110 (76-165)	114 (81-169)	79 (59-160)	.37
LDL Cholesterol (mg/dL)	98 (78-125)	45 (38-56)	50 (33-75)	.93
HDL Cholesterol (mg/dL)	51 (38-67)	46 (38-60)	58 (42-75)	.02
ACC ASCVD 10-y risk score (%)	8.3 (2.9-14.8)	9.4 (5.0-18.7)	2.7 (1.6-11.8)	.005

[a]ACC = American College of Cardiology; ACS = acute coronary syndrome; ASCVD = atherosclerotic cerebrovascular disease; BMI = body mass index; CAD = coronary artery disease; CKD = chronic kidney disease; CVA = cerebrovascular accident; DBP = diastolic blood pressure; HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein; PVD = peripheral vascular disease; SBP = systolic blood pressure; TIA = transient ischemic attack.
[b]Values are mean (IQR) or n (%).

recognition and for automatic classification between healthy and impaired voices.[13-15] The input for computation of the MFCCs is a speech signal that is further analyzed using the Fourier transform mathematical function. Overall, 81 different prespecified voice features were extracted and documented for each recording (R1, R2, and R3) for each patient. Preliminary observations suggested that calculated average and/or maximal voice intensity functions might be associated with multiple disease states, including heart disease.[8] The validity of some of these functions was further evaluated in a clinical study of patients with autistic disorders. Based on these preliminary observations, 81 voice feature functions were preselected to be used in this study.

Study End Point

The primary end point of the current study was the presence of CAD, defined as angiographically determined stenosis of any degree present in at least 1 of 7 predetermined coronary vessels (right coronary, posterior descending, left main, left anterior descending, circumflex, and the 2 obtuse marginal arteries) documented as present or absent (binary variable). Coronary artery disease was further divided into 3 categories: mild (≥30% stenosis), moderate (≥50% stenosis), and severe (≥70%). All angiograms were reviewed by a single investigator who was blinded to patient clinical and voice data.

Statistical Analyses

Data are presented as mean ± SD for normally distributed continuous variables, as median with interquartile range (IQR) for continuous variables that are not normally distributed, and as frequency (%) for categorical variables. In the primary analysis, study population was divided into 2 groups: CAD vs normal

TABLE 2. Results of Univariate Binary Logistic Regression[a,b]

	Recording 1			Recording 2			Recording 3		
Feature no.	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
15	1.05	0.65-1.69	.84	1.78	1.02-3.36	.04	1.72	0.94-3.16	.08
43	2.05	1.03-4.54	.04	1.49	0.62-3.58	.38	1.46	0.77-2.78	.25
49	0.82	0.49-1.38	.46	0.55	0.31-0.98	.04	.61	0.36-1.05	.06
71	0.70	0.41-1.21	.20	0.52	0.29-0.93	.03	.57	0.34-0.95	.03
78	0.79	0.46-1.35	.39	0.60	0.34-0.99	.05	.80	0.44-1.46	.43

[a]OR = odds ratio.
[b]Only voice features with $P < .1$ for at least 1 of the 3 comparisons (R1, R2, or R3) are included in this table.

coronaries. The 10-year ASCVD risk score was calculated according to the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk.[1] Voice features were normalized before the statistical analysis. Continuous parameters of the study groups were compared using the student *t* test. For comparison of categorical data, we used the chi-square and Fisher exact tests. Univariate binary logistic regression was used to estimate the odds ratio for CAD of candidate voice characteristics. This univariate model was applied separately for all 81 voice features of the 3 baseline recordings (R1, R2, and R3). Voice features that were found to be considerable in the univariate model were then used in a multivariate binary logistic regression model with adjustment for the 10-year ACC/AHA ASCVD risk score. The ASCVD risk score was used as a continuous variable in the multivariate model and is based on each patient's age, sex, race, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, blood pressure—lowering medication use, diabetes status, and smoking status. For all the above, the type 1 error rate was 0.05 in a 2-sided test and *P* values and CIs were calculated and presented at the 95% confidence level. The statistical analyses were performed with IBM SPSS version 20.0.

RESULTS

Of 166 patients enrolled in the study, 28 (17%) patients had poor baseline voice recording due to background noise or multi-speakers that did not allow voice feature extraction. Final study cohort included 138: 37 control subjects and 101 study subjects with available voice recordings who underwent a diagnostic coronary angiogram. Demographic, clinical, and laboratory data are summarized in Table 1. Median age of the study population was 61 years (IQR, 51-67 years) and 54 (54%) were men. Compared with patients with no CAD, patients with CAD were older (63 years; IQR, 55-68 years vs 53 years; IQR, 42-66 years; P=.003) and more likely to be treated for hypertension (54% vs 23%; P=.005) or hyperlipidemia (48% vs 23%; P=.02) and have chronic kidney disease (44% vs 20%; P=.02). Consistently, patients with CAD had a significantly higher 10-year ASCVD risk score (9.4% vs 2.7%; P=.005). There were 30 patients with normal coronary arteries, 30 patients with mild CAD, 12 patients with moderate CAD, and 29 patients with severe CAD. For the primary analysis, 71 (71%) patients had CAD.

Univariate and Multivariate Binary Logistic Regression Models

Univariate binary logistic regression model of the 81 voice features revealed 5 voice features that were associated with CAD in at least 1 of the 3 baseline recordings (P<.05 for all; Table 2). The model was used separately for recordings R1 (neutral text), R2 (negative experience), and R3 (positive experience). There were no statistically significant differences between healthy subjects and patients with CAD with respect to the remaining 76 features (P>.05 for all; data not shown). While only 1 voice feature from the first recording (R1) was associated with CAD in this model, voice features of recordings R2 and R3 demonstrated multiple candidate features that were associated with

TABLE 3. Results of Multivariate Analysis With Adjustment for ASCVD Risk Score[a,b]

	Recording 1			Recording 2 (positive experience)			Recording 3 (negative experience)		
Feature no.	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
15	1.421	0.77-2.62	.26	1.516	0.74-3.11	.26	1.778	0.87-3.62	.11
43	1.700	0.73-3.94	.22	2.306	0.79-6.70	.13	3.504	1.10-11.22	.04
49	0.614	0.33-1.15	.13	0.609	0.32-1.17	.14	0.579	0.31-1.09	.09
71	0.720	0.39-1.33	.30	0.412	0.21-0.83	.01	0.605	0.34-1.01	.09
78	0.428	0.43-1.43	.78	0.715	0.39-1.34	.29	0.898	0.43-1.87	.78

[a]ASCVD = atherosclerotic cerebrovascular disease; OR = odds ratio.
[b]Only voice features with $P < .1$ for at least 1 of the 3 comparisons (R1, R2, or R3) are included in this table.

TABLE 4. Results of Multivariate Analysis of Features 43 and 71[a,b]

Recording	OR	95% CI	*P*
Recording 1			
Feature 43	1.97	0.81-4.80	.14
Feature 71	0.63	0.32-1.22	.17
Recording 2			
Feature 43	2.79	0.90-8.62	.08
Feature 71	0.37	0.18-0.79	.009
Recording 3			
Feature 43	4.01	1.25-12.84	.02
Feature 71	0.49	0.25-0.96	.04

[a]ASCVD = atherosclerotic cerebrovascular disease; OR = odds ratio.
[b]All 3 models are adjusted for ASCVD risk score.

CAD in this univariate model ($P<.05$ for all). Candidate voice features that were associated with CAD in the univariate model were then used in a multivariate binary logistic regression model with prespecified adjustment for the ASCVD risk score. The results of this model are summarized in Table 3 and show no association between voice and CAD when patients read a neutral text (R1). However, 2 features were found to be strongly associated with CAD when emotional voice recordings were analyzed: each SD increase in feature 71 was significantly associated with 59% decreased odds of CAD when describing a positive emotional experience (95% CI, 0.21-0.83; $P=.01$) and each SD increase in feature 43 was associated with a significant 3.5-fold increased odds of CAD when describing a negative emotional experience (95% CI, 1.10-11.22; $P=.04$). Finally, both features were evaluated in the same multivariate model separately for the 3 recordings (Table 4). This model consistently showed that both feature 43 and 71 were independently associated with CAD and that the association was significant only when patients were asked to describe an emotionally significant experience: each SD increase in feature 43 of recording 2 was associated with a significant 63% decreased odds of CAD and each SD increase in feature 71 of recording 3 was associated with a significant 4-fold increase in the odds of CAD ($P=.009$ and $P=.02$, respectively).

There were no discernable differences in voice features between patients with or without left main disease (7 vs 94 patients) and between patients who did or did not undergo coronary revascularization due to occlusive coronary disease (21 vs 80 patients). In addition, no graded effect of voice features 43 and/or 71 was identified when patients with CAD were further divided by disease grade (mild, moderate, or severe) or by extent of coronary disease (1-, 2-, or 3-vessel disease).

Voice Features in CAD and Control Groups

Feature 71 is a statistical operator describing extreme values of MFCC. It measures craters around specific frequency bands, and quantifies the width and depth of these craters. It is the only feature that was found to be statistically significant in the multivariate model in both the positive and negative emotional voice recordings ($P=.009$ and $P=.04$, respectively). Figure 1 shows a graphic example of the power spectrum density plots of patients with and without CAD. Figure 2 shows histograms with the distribution of the feature among patients with and without CAD. There were no statistically significant differences in this voice feature between patients with normal coronaries, healthy volunteers, and noncardiac procedure groups. This was true for the first recording (-0.03 ± 0.83 vs -0.02 ± 0.69 vs -0.23 ± 1.07, respectively; $P=.67$), for the emotional positive recording (0.20 ± 0.81 vs 0.14 ± 0.71 vs -0.03 ± 0.97, respectively; $P=.63$), and for the emotional negative recording (0.31 ± 0.87 vs 0.16 ± 0.76 vs -0.05 ± 0.98, respectively; $P=.36$). A second voice feature, feature 43, was also found to be independently associated with CAD in the multivariate model (in the third recording only). It is a skewness measure that portrays the asymmetry of intensity distribution in a specific voice frequency band. It is equivalent to the measurement of the difference between the median and the mean of the intensity distribution. There were no statistically significant differences in this voice feature between patients with normal coronaries, healthy volunteers, and noncardiac procedure groups.

DISCUSSION

The current study has 3 important observations. First, this is the first study to describe an association between voice characteristics and CAD: we identified 5 voice features that were associated with CAD. Voice analysis was

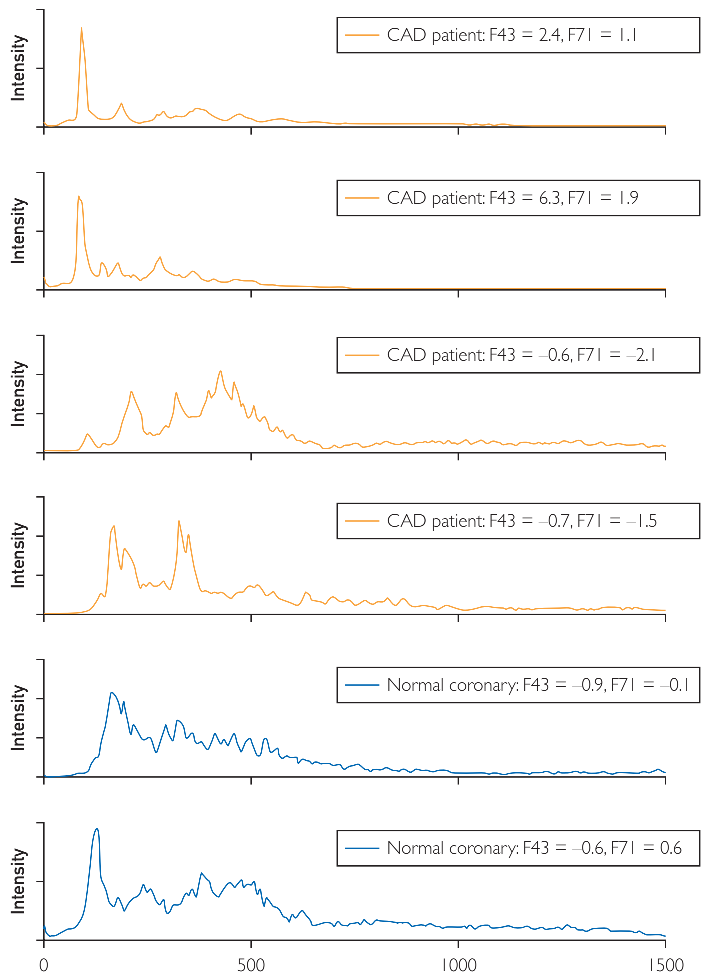

FIGURE 1. Power spectrum density plots of patients with CAD and controls. Examples of PSD of patients with and without CAD. All examples are from the third recording (negative emotional experience). The graphs show cases of patients with normal coronaries, patients with extreme decay/asymmetry of feature 43, and patients with extreme values of feature 71. Features are calculated by averaging over time the instantaneous PSD values calculated using Fourier transform on 25-ms frames with 10-ms shift. CAD = coronary artery disease; PSD = power spectrum density.

performed in a blinded fashion, all voice features were prespecified, and CAD was confirmed with coronary angiogram. Second, the strongest association between voice and CAD was observed when patients were requested to record their voice while describing an emotional experience. The third important observation is that the association was found to be independent of age, sex, and other traditional cardiovascular risk factors that are used in the ACC/AHA ASCVD risk score.

Voice samples analysis in the current study was based on the MFCCs that are used for digital processing of speech signal and based on the Fourier transform mathematical function.[16] This function is ubiquitous in nature.[17] Eyes and ears are essentially using the Fourier transform to interpret sound and light waves. By converting data variation over time into patterns of repetition (frequency), Fourier transform helps in identifying important mechanisms in biological systems. Moreover, methods based on the Fourier transform are used in virtually all areas of engineering and science: signal processing and communication, imaging, crystallography, spectroscopy, to name a few.[17] Our study, which uses Fourier transform analysis to identify a biological phenomenon (ie, CAD), extends and supports previous observation on the important role of Fourier transform in nature.

The current study suggests an association between voice and coronary atherosclerosis. Recently, voice signal analysis has been assessed as a possible clinical diagnostic tool. Using methods similar to the one described in the current study, Bonneh et al[9] analyzed voice samples of 83 children (41 with autistic disorder and 42 controls) and successfully showed that voice signal analysis can be used to identify autistic disorders with a success rate of 86%. Similarly, Parker et al[18] used MFCC voice features to differentiate paroxysmal coughing from pertussis among 47 children (16 examples of nonpertussis coughs and 31 examples of pertussis coughs) with 90% success rate. Benba et al[19] studied voice samples of 34 subjects including 17 patients with Parkinson disease, and achieved a diagnostic accuracy of 91% using the first 12 coefficients of the MFCC. Our findings extend these previous observations by suggesting an association between voice and a systemic inflammatory process—atherosclerosis.[11] We used coronary angiography, the reference standard method for diagnosing coronary atherosclerosis. As a systemic process CAD is often associated with pathologic processes such as chronic kidney disease, cerebrovascular disease, vascular dementia, retinopathy, and peripheral artery disease. Although this study does not propose a biological mechanism that associates voice with atherosclerosis, such a mechanism is plausible given the systemic nature of atherosclerosis and its impact and deleterious effect on all other organs.

An important observation of the current study is that the strongest association between voice and CAD was identified when patients were asked to describe an emotional experience. This finding is supported by previous multiple studies that showed how emotional disturbance is a considerable risk factor for CAD.[20] One possible explanation for our interesting finding is the documented association between mental stress, the adrenergic system, and voice.[21] Emotional stress conditions change the human voice, including an increase in fundamental frequency.[22,23] Giddens et al[24] demonstrated in a double-blind, placebo-controlled study an association between increase in voice jitter and beta adrenergic receptors blockade with propranolol among healthy men and women (N=12). Therefore, one possible hypothesis to interpret our findings is that the association between voice and atherosclerosis is mediated by hypersensitivity of the adrenergic system to stress. The association between stress, the adrenergic system, and atherosclerosis is well established on the basis of robust data.[25] Based on this known association, it may be suggested that the voice characteristics identified in this study are an index of underlying stress and adrenergic activity that correlate to CAD. Moreover, by identifying subjects with relatively high sensitivity to emotional stress, our voice analysis algorithm might help in quantifying stress and identifying patients with high pretest probability for CAD. This is also supported by the observation that the association documented in this study was independent of age, sex, and the traditional cardiovascular risk factors incorporated in the Framingham risk score. Hence, this voice feature might be a marker of stress, an important cardiovascular risk factor that is not included in the Framingham score.

This study suggests a potential relationship between voice characteristics and CAD. Study strengths include the use of coronary angiogram to define atherosclerosis, the blinded analysis of the voice data, and the analysis of prespecified voice features. However, this study has several limitations. First, this study reports association only and lacks evidence on the underlying mechanism. Second, this is a preliminary small observational study that included relatively middle-aged white subjects. Further research in larger and more diverse populations is needed to generalize our results and to confirm the reproducibility of our findings. Third, all voice recordings were performed in the English language. There is a need for future studies to validate the consistency of our findings in other languages. Last, the quality of voice recording needs to be improved to increase the utility of this novel approach.

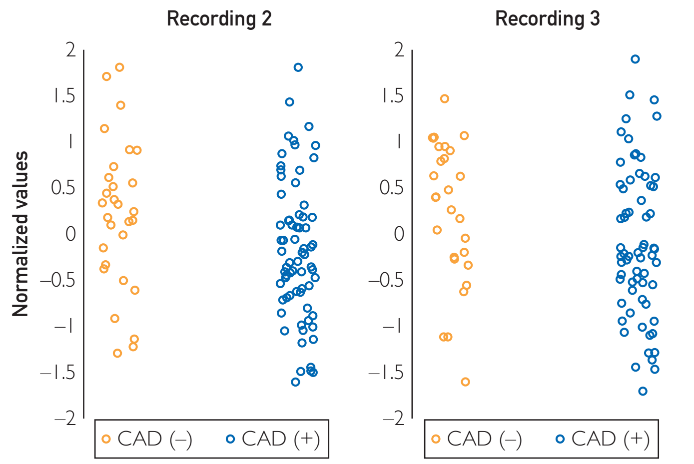

FIGURE 2. Histogram of feature 71 of recordings 2 and 3. The figure shows the distribution of normalized values of voice feature 71 during the second and third recordings among patients with and without CAD. For the second recording, the mean normalized values were -0.20 ± 0.75 vs 0.20 ± 0.81 among patients with and without CAD, respectively (P=.03). For the third recording, the mean normalized values were -0.14 ± 0.91 vs 0.31 ± 0.87 among patients with and without CAD, respectively (P=.03). CAD = coronary artery disease.

CONCLUSION

This is the first study to suggest an association between voice characteristics and CAD. Voice features analysis holds the potential to assist physicians in estimating the pretest probability of CAD among patients presenting with chest pain, especially in the setting of telemedicine—when clinical health care is provided at a distance.

Abbreviations and Acronyms: **ACC** = American College of Cardiology; **AHA** = American Heart Association; **ASCVD** = atherosclerotic cerebrovascular disease; **CAD** = coronary artery disease; **IQR** = interquartile range; **MFCC** = Mel Frequency Cepstral Coefficient

Potential Competing Interests: The authors report no competing interests.

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