

A novel approach to diagnosing coronary artery disease: acoustic detection of coronary turbulence

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Abstract Atherosclerotic disease within coronary arteries causes disruption of normal, laminar flow and generates flow turbulence. The characteristic acoustic waves generated by coronary turbulence serve as a novel diagnostic target. The frequency range and timing of microbruits associated with obstructive coronary artery disease (CAD) have been characterized. Technological advancements in sensor, data filtering and analytic capabilities may allow use of intracoronary turbulence for diagnostic and risk stratification purposes. Acoustic detection (AD) systems are based on the premise that the faint auditory signature of obstructive CAD can be isolated and analyzed to provide a new approach to noninvasive testing. The cardiac sonospectrographic analyzer, CADence, and CADScore systems are early-stage, investigational and commercialized examples of AD systems, with the latter two currently undergoing

clinical testing with validation of accuracy using computed tomography and invasive angiography. Noninvasive imaging accounts for a large percentage of healthcare expenditures for cardiovascular disease in the developed world, and the growing burden of CAD will disproportionately affect areas in the developing world. AD is a portable, radiation-free, cost-effective method with the potential to provide accurate diagnosis or exclusion of significant CAD. AD represents a model for digital, miniaturized, and internet-connected diagnostic technologies.

Keywords Coronary artery disease · Acoustic cardiography · Stress testing

Introduction

According to a recent report, cardiovascular disease (CVD) persists as the leading cause of premature death in the developed world [1]. Moreover, CVD is increasing globally with approximately two-thirds of all CVD deaths now occurring in the developing world. In all regions, diagnostic testing is responsible for a large proportion of health care costs. In this context, there is necessity for alternative and cost-effective methods to diagnose coronary artery disease (CAD).

Stress modalities were developed to assess cardiac physiology in both diseased and non-diseased states. The specific endpoint of the various tests is to detect either the electrical, functional or perfusion abnormalities associated with ischemia and significant CAD. These tests assess the downstream physiologic consequences of obstructive CAD rather than specific intracoronary disturbances. In contrast, invasive techniques such as fractional flow reserve (FFR) do directly assess intracoronary physiology. The measurement of pressure changes across stenotic lesions has been widely

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integrated into clinical practice and treatment guidelines [2–4]. A noninvasive correlate to FFR using offline analysis of cardiac CTA images has recently become available [5, 6].

The use of FFR is the prime example of the clinical application of physiologic testing within the microenvironment of the coronary artery. Abnormal flow patterns also occur within this microenvironment but have not been previously utilized for diagnostic purposes. The phenomenon of flow turbulence has been recognized as a feature of obstructive CAD for decades. The novel method of acoustic detection (AD) is based on the premise that the acoustic signature of turbulent coronary flow can be detected, analyzed and used for clinical purposes.

Recent advances in noninvasive testing for CVD are best characterized as iterative improvements upon well-established technologies—electrocardiography, ultrasound, nuclear perfusion, magnetic resonance, and computed tomography. In that context, these common tests may appear dated in comparison to the dramatic evolution of miniaturized, digital, and internet-connected technologies used in both medical and non-medical fields.

There are numerous potential benefits to utilizing coronary turbulence as a physiologic target in testing and diagnosis. Novel handheld devices may substantially improve resource utilization, efficiency, portability, access, and cost. AD is also a radiation-free technology. From a healthcare delivery perspective, risk stratification using AD has the potential to efficiently improve care pathways and more judicious use of intensive or invasive studies.

Background

In 1967, Dock and Zoneraich reported a patient with a murmur that they ascribed to a severe stenosis in the left anterior descending artery. The timing of the murmur (frequency range 80–240 Hz) coincided with peak coronary flow in diastole. Though this physical finding is not widely appreciated, the angiographic and phonocardiographic data included in their paper provide reasonable support for their conclusion [7].

Other authors have described similar cardiac murmurs attributed to coronary disease [8, 9]. Nonetheless, the Dock's murmur has been of little clinical utility and questionable provenance over the last five decades. It is possible that a murmur was incorrectly associated with a coronary lesion. Alternatively, the origin of the murmur was correctly described but flow turbulence is typically beyond the limits of human audition aided by a traditional stethoscope.

Auscultation of turbulent flow is a common method for bedside diagnosis. Detection of Korotkoff sounds with a manual sphygmomanometer and stethoscope to measure blood pressure has only recently been widely replaced with

automated systems. Listening for heart sounds, valvular murmurs, carotid bruits and radiated murmurs is an integral part of the physical exam. The superficial and relatively large carotid artery is ideal for detecting turbulent flow with the aid of the stethoscope. In contrast, the relatively small coronary arteries are deep, in motion, and surrounded by competing noise from the contents of the thorax.

Evidence development

Disruption of laminar coronary flow occurs beyond significant obstructions. Sufficient velocity of flow is required for flow lamina to break apart. However, there is not a gradual increase in turbulence as velocity increases. Turbulence occurs when a critical Reynolds number (Re) is exceeded with this value representing the ideal conditions for flow disruption. Re increases with velocity, decreases with viscosity, and is affected by vessel diameter. The Re is relatively low in straight, smooth blood vessels. In vessels with significant atherosclerotic plaques, the critical Reynolds number is much higher. In these instances, turbulence may occur even at normal physiologic flow velocities.

The flow at a coronary stenosis was described by Fredberg as a converging–diverging nozzle with flow acceleration at the point of smallest cross-sectional area and, beyond that point, separation of flow from the vessel wall in a recirculating pattern [10]. Laminar coronary flow is disrupted by friction and the creation of eddy currents distal to a lesion (Fig. 1). This turbulent flow releases kinetic energy in the form of heat and acoustic mechanical waves.

Despite historical reports of audible murmurs, the acoustic characteristics of turbulent coronary flow are exceedingly complex. Capitalizing on this phenomenon requires a thorough understanding of the frequency, amplitude, and timing of the sound waves. Competing sound spectra must be identifiable and excluded. Furthermore, AD requires an optimal process to detect, filter and analyze the collected data.

Early reports described both low- and high-pitched murmurs associated with CAD [7, 8]. Phonocardiographic studies long-ago described the characteristics of valve closure sounds and valvular murmurs [11]. In general, these non-coronary artery noises occupy the 10–400 Hz range.



Fig. 1 Disruption of laminar flow by a coronary stenosis

Coronary turbulence has an overlapping spectral range between 10 and 800 Hz. Akay, Schmidt and others have provided seminal information on the frequency range associated with CAD (Table 1) and their conclusions have been validated using coronary angiography [12–20].

Two important experimental approaches support the reported frequency ranges for coronary turbulence. Borisyuk designed a model of vascular stenosis to study these acoustic properties. Though data was obtained at steady flow rather than the pulsatile flow pattern of the coronary tree, he elegantly demonstrated the complexities of trans-stenotic flow and the multiple frequency bands below 200 Hz associated with a simulated vascular stenosis (Fig. 2) [21].

Pre- and post-angioplasty data also helps confirm that acoustic frequencies associated with significant CAD are attributable to the obstructive lesions. Akay et al. analyzed ten subjects before and after coronary angioplasty [13]. The blinded analysis of the frequency data correctly classified eight of ten cases as either pre- or post-angioplasty. In the same series, this early AD process correctly classified an additional 17 of 20 subjects as normal or diseased with characteristic frequency spectra >400 Hz.

Table 1 Spectral frequency ranges associated with obstructive CAD

Author	Subjects (n)	Frequency range (Hz)
Akay et al. [13]	30	>400
Akay et al. [14]	20	400–800
Akay et al. [17]	43	>400
Akay et al. [18]	80	>300–800
Schmidt et al. [19]	132	<100
Schmidt et al. [20]	133	<100

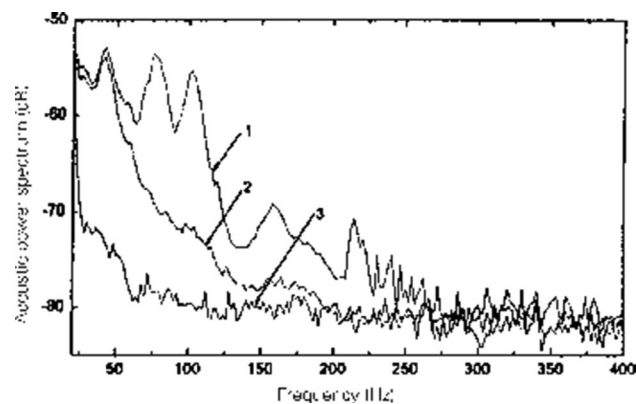


Fig. 2 In vitro modeling of acoustic patterns of vascular stenosis legend 1—stenosis 2—normal 3—background noise reproduced with permission Borisyuk, AO. Experimental study of noise produced by steady flow through a simulated vascular stenosis. Journal of Sound and Vibration 2002

The similarity in frequency between valve closure sounds, valvular murmurs and intracoronary bruits is a significant potential confounder for AD. All AD approaches primarily focus on the diastolic period thus obviating potential interference from heart sounds and common systolic murmurs. It is unknown whether diastolic murmurs originating from mitral stenosis or aortic regurgitation would affect the accuracy of AD in analyzing the diastolic period.

The timing of peak coronary turbulence in diastole relative to the second heart sound provides a consistent reference point for sound detection. The sounds of disrupted flow in the coronary tree are most pronounced in diastole with a peak signal that should theoretically occur 200–300 ms after the second heart sound, coinciding with the maximal coronary flow at mid diastole. Cheng reported the sound occurred 80 ms after the second heart sound (S2) [8]. Akay et al. have cited a segment 200–300 ms after S2 for optimal discrimination [18]. Schmidt reported AD data isolated 150 ms after S2 [19]. Graphical representation of the characteristic diastolic spectral signal is shown in Fig. 3.

AD systems

Since the acoustic signature of coronary turbulence is too faint for the unaided ear, specialized microphone sensors or stethoscopes are required. The sensor to skin interface requires specific considerations for impedance matching, pressure application and exclusion of background noise.

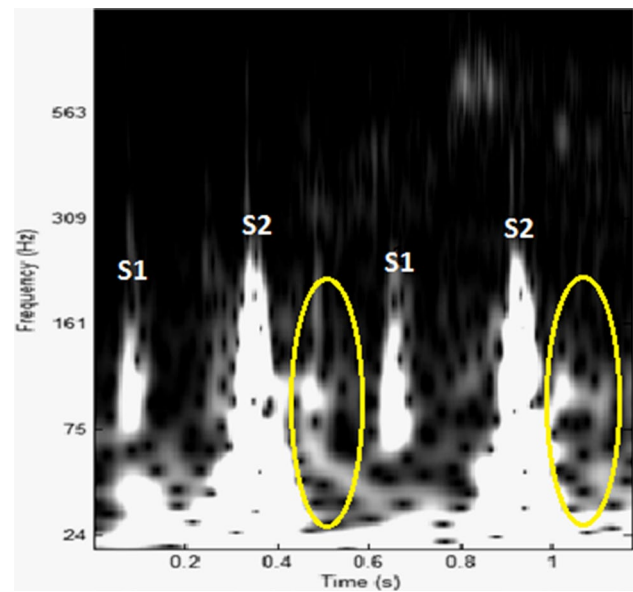


Fig. 3 Graphical example of sound spectra associated with CAD legend S1 (first heart sound), S2 (second heart sound). Characteristic diastolic low frequency spectral activity associated with right coronary artery stenosis (yellow ovals). Reproduced with permission AUM Cardiovascular, Inc., Northfield, Minnesota

Furthermore, even after amplification of the emanated noise, coronary turbulence is buried in the competing sounds of the cardiac and thoracic structures. Performance of all AD tests requires a quiet environment to minimize interference.

An effective AD method requires data-filtering algorithms and analytics to isolate the specific target signals used for diagnosis. The AD systems that have been studied or are currently in development utilize different sensor designs and various filtering processes. The reported target frequencies for classifying coronary turbulence are highly variable between systems, reflecting the range of attributed frequency (as in Table 1) and proprietary nature of the early-generation analytic systems. Two systems have been recently approved for use in Europe.

Cardiac sonospectrographic analyzer

Building on the work of pioneers Semmlow, Akay et al., the cardiac sonospectrographic analyzer (CSA, SonoMedica Inc., Vienna, Virginia) is an AD system designed to predict or exclude significant CAD based on the presence of coronary turbulence or microbruits. CSA uses an FDA-approved digital electronic stethoscope system designed to detect noises in the 400–2700 Hz range and this sensor is coupled to a computer to complete the investigational CSA analysis [22].

CSA analysis involves auscultation of microbruits at nine chest-wall sites (Fig. 4). The transducer records for 40 s at each position with simultaneous electrocardiographic-gating using four surface electrocardiographic leads. Unique to this AD method, there is potential anatomic localization

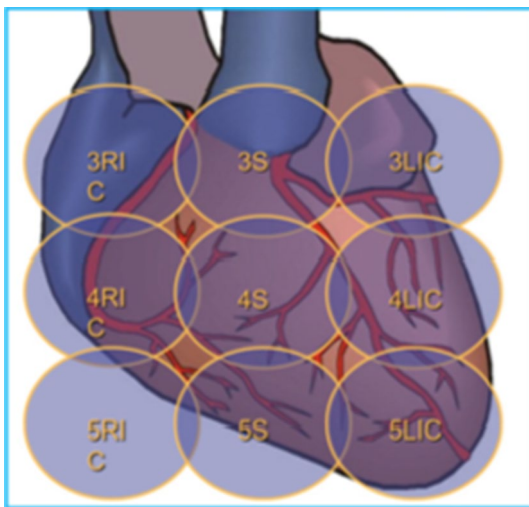


Fig. 4 Cardiac sonospectrographic analyzer sensor locations and testing protocol reproduced with permission Makaryus, Utility of an advanced digital electronic stethoscope in the diagnosis of coronary artery disease compared with coronary computed tomographic angiography. *Am J Cardiol* 2013

of coronary lesions based on differential signals at various locations.

The filtered and analyzed CSA data is compiled into a microbruit score (MBS). The MBS can be calculated for each of the nine individual readings and also as a cumulative average of the separate readings. In the published clinical investigation, the MBS was presented in a range of 0–1, where 0 represented a low probability and 1 represented a high probability of significant CAD.

The diagnostic accuracy of CSA was reported in a study of 200 subjects with no prior history of CAD who were referred for cardiac CTA. Subjects underwent CSA prior to CTA. 29 had inadequate or absent CSA data leaving 161 in the per protocol analysis [22].

There was a direct correlation between total MBS score and extent of CAD. The prevalence of significant CAD (>50% diameter stenosis) in this cohort was 12%. MBS scores above the threshold predictive of CAD correctly identified 17 of 19 of subjects with significant CAD (sensitivity 89.5%) and specificity of 57.7%. The receiver operating characteristics AUC at 0.74 was in line with other stress modalities. The demonstrated sensitivity supports the potential utility of AD, although the enrolled chest pain population had a relatively low rate (12%) of significant disease by CTA.

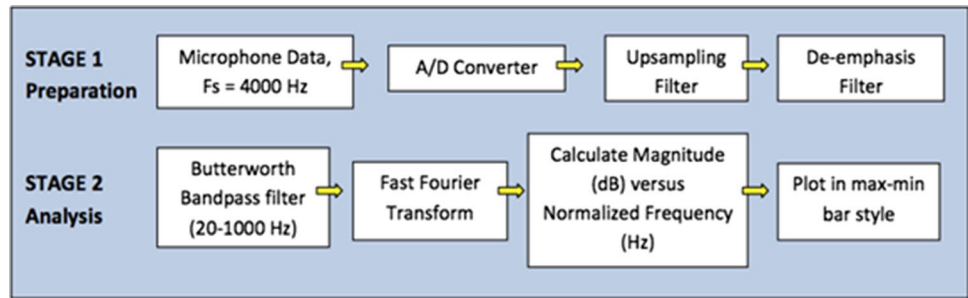
CADence system

Early data supporting the CADence device (AUM Cardiovascular Inc., Northfield, Minnesota) is derived from the work of Guion-Johnson at the University of Minnesota. Using a commercially-available digital electronic stethoscope, the derived process of data filtering and analysis is depicted in Fig. 5 [23]. The sound acquisition and processing sequences are similar among AD systems although each AD method has specific, proprietary components that give rise to unique performance characteristics and preclude generalization between systems.

The initial work focused specifically on the historical Dock's murmur lesion of the left anterior descending artery at a target frequency range of 100–800 Hz. A total of 51 subjects were studied prior to clinically-indicated coronary angiography. AD detected severe coronary obstructions in 17 subjects with a diagnostic accuracy of 76% [23].

The ACOUSTIC trial is the largest reported series using this technology. In this experience, diagnostic accuracy was reported for all major epicardial coronary arteries. One hundred and fifty-six subjects were studied prior to coronary angiography and 123 had both angiographic and AD data available for analysis. Sensitivity and specificity to detect CAD ($\geq 50\%$ diameter stenosis in vessels ≥ 2.5 mm in diameter) were 70 and 80%, respectively [24].

Fig. 5 Acoustic detection data filtering and analytic process adapted from Guion-Johnson MA. Using digital stethoscope data to diagnose stenosis in the left anterior descending coronary artery. *Circulation* 2006; 114 (Suppl 2):600



The current CADence sensor is a highly-engineered device that incorporates a microphone sensor, ambient noise management and data pre-filtering. The handheld device uses wireless technology to transfer acoustic data to a cloud-based analytic engine. Clinical efficacy data has not yet been published using this latest system.

The CADence testing protocol uses a patient specific booklet to initiate and sequence the study and provide a tracking code for the de-identified patient data (Fig. 6). The handheld device provides user feedback indicating adequate patient skin contact and signal detection. Data is collected at four chest wall sites with each reading taking 30 s. After upload and analysis, the results are electronically returned to the clinician in under 10 min. The diagnostic conclusions are classified as either negative, positive or inconclusive for turbulence associated with obstructive CAD [24].

A pivotal study using CADence AD is currently enrolling up to 1200 subjects with chest pain and multiple cardiovascular risk factors. TURBULENCE (NCT01743040) will validate the diagnostic accuracy of CADence versus the anatomic gold-standard tests, cardiac CTA and invasive

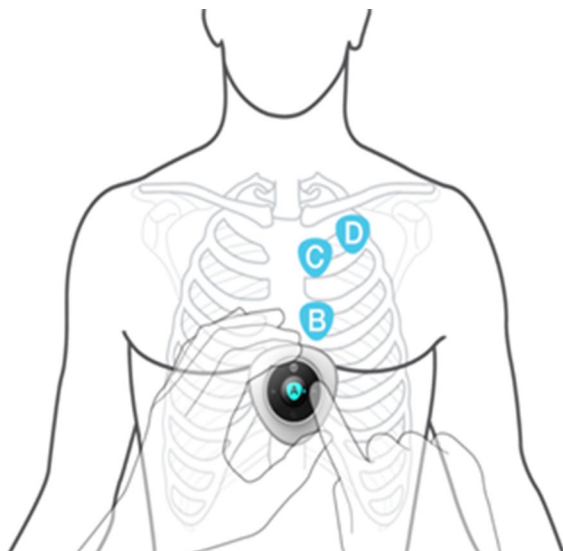


Fig. 6 CADence handheld device and testing sequence reproduced with permission, <http://www.aumcardio.com> and AUM cardiovascular, Inc., Northfield, Minnesota

angiography. The primary endpoint is non-inferiority of AD as compared to an objective performance criteria representing the performance of nuclear perfusion testing to detect $\geq 70\%$ stenosis in any major epicardial vessel or $\geq 50\%$ in the left main coronary artery [25].

CADScore system

Another method to predict CAD risk using AD has been developed by collaborators at Aalborg University (Denmark) and Acarix A/S (Kongens Lyngby, Denmark). This group has reported extensively on specific detection and computational methods developed for AD [26, 27]. Schmidt et al. studied a total of 265 subjects in two studies prior to coronary angiography using a novel sensor and analytic software [19, 20]. Of note, while the discriminant frequencies ascribed to coronary turbulence have been reported at >300 – 400 Hz, their analyses found a shift to lower frequency ranges (>100 Hz) depending on the computational method.

The CADScore system is comprised of a palm-sized acoustic analyzer with a flexible connection to an adhesive sensor that is applied to the chest wall at the fourth left intercostal space (Figs. 7, 8). There is a separate base console that recharges and calibrates the analyzer. A 3 min recording is performed on the supine patient with 4 separate breath holds to reduce acoustic interference. Findings are reported numerically along a continuum of risk (low, <20 ; intermediate 20 – 30 ; high >30) [28].

The analytic process of the CADScore system includes both the low (<100 Hz) and also high (>200 Hz) frequency ranges. Unique to this AD method, the intensity of the fourth heart sound is additionally incorporated as a predictive variable.

The performance of CADScore has recently been reported in a large cohort of subjects undergoing cardiac CTA and coronary angiography. All subjects had quantitative coronary artery calcium (CAC) scoring, and the accuracy of CADScore was compared to a traditional clinical risk calculator, CAC, and various combinations of AD, clinical risk and CAC [29].

A total of 255 subjects were included though AD results were incomplete in 21 subjects due to weak signals, excess

Fig. 7 CADScore analyzer, base console and sensor reproduced with permission, <http://acarix.com>, Acarix A/S, Kongens Lyngby, Denmark



Fig. 8 CADScore sensor location and testing protocol reproduced with permission Winther S, Diagnosing coronary artery disease by sound analysis from coronary stenosis induced turbulent blood flow: diagnostic performance in patients with stable angina pectoris. *Int J Cardiovasc Imaging* 2015



ambient noise and arrhythmia that prevented acoustic analysis. Sixty-three had significant CAD ($\geq 50\%$ stenosis) on angiography. The diagnostic accuracy of CADScore for significant CAD by AUC was 0.72. This was similar to the Diamond-Forrester clinical risk score (AUC 0.79, $p = \text{ns}$) and significantly lower than for CAC (AUC 0.86, $p < 0.01$). The combination of CADScore and clinical risk were additive with a diagnostic AUC of 0.82 that was significantly better than either measure alone.

The optimal CADScore for binary determination of CAD was determined to be 24.2 with a sensitivity and specificity of 76 and 59%, respectively. A low risk CADScore (< 20) had a negative predictive value of 92.5%, supporting the authors' suggestion that it might serve as a rule-out test screening patients proximal to traditional noninvasive studies. When the CADScore was combined with the Diamond-Forrester score, a significant improvement in risk stratification was demonstrated with a net reclassification index of 0.31 [29].

The performance of the CADScore is being evaluated in the Danish study of noninvasive diagnostic testing in coronary artery disease (NCT02264717). 2000 subjects undergoing cardiac CTA will be enrolled to evaluate the accuracy of this system in a population with an intermediate pre-test probability of CAD. In addition, those subjects progressing to clinically-indicated invasive angiography will undergo FFR testing and also be randomized to cardiac MRI or nuclear perfusion study. The performance of AD will be

compared to CTA and invasive angiography as part of the study's secondary endpoint [30].

Two of the AD technologies (CADence and CADScore) are completing large blinded trials evaluating diagnostic accuracy. There are no further studies identified evaluating the Sonomedica CSA system. In total, the early studies include full data on 512 subjects with validation of results using either cardiac CTA and invasive angiography (Table 2). Data on up to 3000 additional subjects is forthcoming and should provide critical insight into the future of AD.

Discussion

Coronary turbulence is a novel diagnostic target being studied as a potential method to detect CAD. The current state of sensor and analytic power is poised to enable development and validation of AD as a diagnostic and risk stratification tool. Considering that Dock first described a murmur associated with coronary stenosis nearly 50 years ago, it is possible that only contemporary technologies may now allow its assessment. If AD is proven sufficiently accurate in ongoing studies, it is a reasonable assumption that the tools available in previous decades simply lacked the sophistication to take advantage of the acoustic signature of CAD.

The limited data on nascent AD systems suggests that diagnostic accuracy is comparable to other noninvasive

Table 2 Studies evaluating diagnostic accuracy of AD

Author, year	Device	Target frequency (Hz)	CAD definition	Subjects (n)	CAD prevalence	Sens	Spec
Makaryus et al. [22]	Sonomedica	400–2700	>50% stenosis by CTA	161	12%	0.89	0.58
Winther et al. [31]	CADScore	20–1000	>50% stenosis by CTA, Angio	228	27%	0.76	0.59
Azimpour et al. [29]	CADence	20–2000	>50% stenosis by Angio	123	52%	0.70	0.80
Dan-NICAD	CADScore	20–1000	>50% stenosis by Angio	2000	Study ongoing, expected 2016		
TURBULENCE	CADence	20–2000	>70% stenosis by CTA, Angio	1000	Enrollment completed 2016		

modalities. In the narrow populations studied, all three systems described herein have 70% or better accuracy. A substantial amount of work remains to enhance their detective and analytic processes and to demonstrate sufficient accuracy in trials involving clinically relevant populations.

There are significant potential limitations inherent to the AD approach. The generation of turbulence requires sufficient flow, theoretically affecting the sensitivity to detect isolated total occlusions without antegrade flow. This question will be challenging to answer due to the low frequency of truly isolated total occlusions without even moderate disease in other coronary vessels. The AD technologies do not to localize the anatomic origin of coronary turbulence or specify individual diseased vessels. While this feature is not incorporated into any of the current technologies, the CSA and CADence systems do utilize multiple chest wall sites that may correspond to specific vessels. The impact of single- versus multi-vessel disease on AD accuracy is unknown. Variable sensitivity and specificity for different vessels and vessel segments is another similar potential confounder. These issues require clarification in large numbers of subjects with angiographic validation.

The effects of heart rate, blood pressure, and other hemodynamic and rheologic factors on coronary turbulence and on the intra-patient reproducibility of AD results are not clear. Patients with noisy chests due to valvular murmurs or lung conditions have generally been excluded from the initial studies so the applicability of AD in these populations is unknown. The two large studies that are in process include patients referred for either nuclear stress testing or cardiac CTA. Thus these datasets will represent primarily stable, intermediate-risk patients with chest pain. While each AD testing protocol is relatively straightforward, proving the scalability and reproducibility of results outside of a clinical trial is a challenge that all new technologies face.

Any future role of AD technologies depends on robust data supporting their diagnostic performance. If successful, radical new pathways in the workup of chest pain syndromes are possible in both outpatient- and hospital-based scenarios. The ability to classify patients as low-risk for obstructive CAD or accurately predict the absence of CAD could position AD as a gatekeeper to further noninvasive or invasive testing. If an AD system is proven sufficiently

accurate, it could supplant various noninvasive methods or serve in the triage of patients to anatomic testing with CTA or invasive angiography.

Cardiovascular diseases account for the largest percentage of healthcare costs in the United States. It is estimated that the direct costs of cardiac care will increase from \$273 to over \$800 billion per year by the year 2030. The total burden could exceed \$1 trillion if indirect costs such as lost productivity are included [32, 33]. Imaging and noninvasive diagnostics make up nearly one-fifth of the direct costs, and the diagnostic yield of stress testing is often low [34–36]. The potential of a technology like AD to reduce imaging costs is attractive in the context of the vast resources expended toward cardiovascular testing.

The greatest challenge for any new technology is meeting the metric of improving patient outcomes. Better tests do not necessarily provide better outcomes, and the focus of imaging research has only recently moved to outcome data rather than pure diagnostic accuracy [37]. AD may have a substantial role in cardiovascular medicine if it can prove some combination of diagnostic equivalence or superiority along with improved efficiency, cost or safety. To that end, AD leverages cutting-edge technology for the detection of the physiologic signature of atherosclerotic coronary lesions. Furthermore, current AD systems provide a window into the future of miniaturized, digital and cloud-based diagnostics.

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Compliance with ethical standards

Conflict of interest SW and RFW have disclosed no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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