Yale Medicine

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EKG Insights, Inc
Re: PlainSight ECG Analysis Algorithm

Introduction

The invention and refinement of the electrocardiogram (ECG) in the first half of the 20th century resulted in tremendous advancements in our understanding of cardiac physiology and pathology [1]. Although the 12 lead ECG in 2021 is now technologically refined and digitally stored compared with the analog paper tracings of the 1950's, the essence of the 12 lead ECG and its clinical interpretation have not fundamentally changed since that time. Over the decades, variations such as vectorcardiograms [2] and signal averaged ECGs have added some additional diagnostic capabilities to the standard 12 lead ECG, but they have never found widespread adoption due to their niche discriminatory utility.

According to claims data, the 12 lead ECG is one of the most commonly billed diagnostic tests in the United States, and likely the world. The FDA has recently approved single and pauci-lead systems for home use by the general public (Apple Watch, KardiaMobile). These pauci-lead systems are suitable for the detection of simple arrhythmias such as atrial fibrillation, but are not designed to diagnose ischemic conditions or other cardiovascular pathology.

Although the 12 lead ECG is the gold standard for the diagnosis of cardiac arrhythmias and acute ST elevation myocardial infarction (STEMI), it is not particularly sensitive nor specific in the diagnosis of left ventricular hypertrophy (LVH), dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), chronic coronary disease, valvular heart disease such as severe aortic stenosis (AS) or mitral regurgitation (MR), or non-ST elevation acute coronary syndromes (NSTE-ACS). These important disease states currently require advanced and expensive diagnostic testing techniques such as echocardiography (echo), stress testing, cardiac magnetic resonance imaging (MRI), and cardiac catheterization (cath). Furthermore, interpretation of 12 lead ECG's is an acquired skill and not necessarily well performed by non-cardiovascular specialists.

The PlainSight algorithm by EKG Insights described in Appendix A utilizes computer software to detect minute changes in the electrocardiographic signal to

reveal additional physiologic information. The full characteristics and applications of the algorithm are not fully elucidated at this time as it has yet to be systematically studied in a large-scale fashion. However, our preliminary studies strongly indicate the algorithm has significant clinical potential.

Methods

We retrospectively analyzed 104 clinically obtained digital 12 lead ECG's using the PlainSight algorithm. Patients had a variety of cardiovascular conditions including normal patients, nonspecific chest pain, acute coronary syndromes, valvular heart disease, cardiomyopathies and COVID-19. The 12 second digital ECG file (DICOM or HTML) was looped 3 times to meet the 30 second data acquisition requirement of the PlainSight algorithm. This generated a "myocardial score" of 0-100 with <20 considered "normal". Scores >=20 are considered abnormal with higher scores indicating more acute physiologic myocardial stress. The PlainSight algorithm has the capability of mapping abnormalities in order to localize potential areas of interest, but the localization data were not examined in this study. The study was approved by the Yale University Institutional Review Board.

Multiple ECG's were available from 3 different patients on the same day (at least 3, as many as 5). Each of the ECG's was subjected to PlainSight and the scores were all within +/- 5 points on the same patient and none were above/below threshold (e.g., scores for an individual patient were all <20 or >=20).

Clinical history including 12 lead ECG interpretation (by the author) and data abstraction were performed (e.g., stress test, echocardiogram, cardiac biomarker, COVID status, cardiac catheterization results). The PlainSight algorithm was applied blindly to the submitted ECG's.

Results

Of the 104 ECGs submitted for analysis, 16 had uninterpretable ECG's for technical reasons. The vast majority of the errors were likely due to artifacts introduced by the "looping" required and not indicative of patient-specific issues. However, 3 patients with left bundle branch block (LBBB) and one patient with a paced rhythm were submitted for analysis and the PlainSight algorithm was uninterpretable. Additionally, 3 patients also had paced rhythms and 1 patient had a LBBB but these patients did yield results using PlainSight.

2 patients had distinct ECG's that were available from the same day that were resubmitted and were analyzable. 14 patients did not have ECG's from the same day. Thus, the total data set was comprised 90 interpretable ECG's which are listed in Appendix B.

Of the 90 patients, 59 were judged to have an acute or severe chronic cardiovascular pathology (e.g., acute coronary syndrome, acute myocarditis/cardiomyopathy, chronic severe valvular heart disease, chronic severe pulmonary hypertension, cardiac tamponade, hypertrophic cardiomyopathy, stable angina with abnormal stress test/cardiac catheterization, acute diastolic heart failure). From Table 1, PlainSight had an overall sensitivity of 76% and specificity of 88% of PlainSight compared with all diagnostic modalities.

Table 1. PlainSight Compared with All Diagnostic Testing

n=90	PlainSight +	PlainSight -
Cardiac Disease +	44	14
Cardiac Disease -	4	28

Of the 14 false negative patients, the clinical scenarios were as follows:
1 pulmonary embolism with RV strain on CT and abnormal troponin
1 COVID + but troponin - with mild cardiomyopathy
1 COVID + and troponin + with mild cardiomyopathy
3 NSTE-ACS with CAD confirmed on cardiac catheterization
4 stable CAD patients with abnormal stress test and chronic CAD confirmed on cardiac catheterization
1 patient with severe aortic stenosis
1 patient with COVID -, troponin + acute myocarditis
1 severe non-ischemic cardiomyopathy

23/90 patients had abnormal cardiac troponin biomarkers. 17/23 had abnormal PlainSight scores (sensitivity 74%).

Of the 4 false positive patients, 3 had evidence of "scarring" on a non-invasive stress test but had no epicardial coronary artery disease on cardiac catheterization. 1 patient was COVID + but had no biomarker evidence of cardiac involvement.

All patients' ECG's were interpreted for acute changes that might be indicative of acute pathology, e.g., significant T wave inversions or ST segment changes in Table 2. Nonspecific changes such as T wave flattening, Q waves, or ECG's

consistent with left ventricular hypertrophy were not considered acute pathology. Using these criteria, the standard lead ECG had a sensitivity of 19% and a specificity of 94% compared with all diagnostic modalities.

Table 2. ECG Compared with All Diagnostic Testing

n=90	ECG +	ECG -
Cardiac Disease +	11	48
Cardiac Disease -	2	29

3 patients had acute pulmonary embolism. PlainSight scores were abnormal in 2/3.

8 patients had valvular heart disease (aortic stenosis or mitral regurgitation). 3 had only mild valvular disease and the PlainSight score was normal in 3/3. The PlainSight score was abnormal in 4/5 patients with severe valvular heart disease.

24/90 ECGs were obtained from COVID+ patients. PlainSight scores were abnormal in 9/24. Of all of the COVID patients, 10 were thought to have cardiac involvement. PlainSight Scores were abnormal in 8/10.

16 patients were either healthy or had remote, stable coronary disease. The PlainSight score was normal in 15/16 (<20). One patient had prior remote CABG and had stable grafts at the time of catheterization with an abnormal PlainSight score (also counted as a false positive).

1 Patient had no symptoms but suffered a NSTEMI after orthopedic surgery. The PlainSight score was normal on an ECG 1 year prior to her surgery and abnormal 1 month immediately prior to her surgery

2 Patients had acute cardiomyopathy. One was thought to be related to chemotherapy and the PlainSight score was abnormal. One was thought to be due to stress (takotsubo syndrome) and the PlainSight score was normal

1 Patient had known hypertrophic cardiomyopathy. PlainSight score was abnormal

1 Patient had known poorly treated hypertension and presented with acute psychosis and severe hypertension. The PlainSight score was abnormal.

2 Patients had cardiac tamponade from a pericardial effusion and both had abnormal PlainSight scores.

Discussion

Despite the very small sample size for this study, the PlainSight algorithm clearly added clinical information that is not readily discernable from the 12 lead ECG or history and physical examination across a diverse range of cardiac pathologies.

PlainSight correlated well with ***advanced*** diagnostic imaging (e.g., cardiac catheterization, echocardiography) and/or serum cardiac biomarkers (i.e., troponin). When judged against any confirmed cardiac abnormalities, the overall sensitivity and specificity of the PlainSight algorithm in this sample are: 76% and 88% which are extremely impressive. For comparison, the standard 12 lead ECG used in this study (which requires interpretation by a trained cardiologist) only had a sensitivity of 19% and in general, standard stress testing has a sensitivity of approximately 65% and specificity of approximately 73% for the detection of significant coronary artery disease.

The PlainSight algorithm is also remarkably specific. A specificity of 88% gives the algorithm a positive predictive value (PPV) of 92% and a negative predictive value (NPV) of 67%.

Most interestingly, as applied in this study, PlainSight appears to be able to detect myocardial abnormalities across a broad spectrum of cardiovascular disease states: cardiomyopathy, valvular heart disease, acute pulmonary embolism, cardiac tamponade, etc. as well as ischemic heart disease. Additional studies will be required but the Amplitude Variability Analysis (AVA) algorithm built-into PlainSight appears to be detecting myocardial stress using surface electrodes. As a screening tool, the PlainSight score may be akin to a “check engine light” or a “pulse oximeter” for the heart. This is especially important when considering this technology for use by non-cardiologists. The PlainSight algorithm is completely software derived from a standard ECG acquisition and it is being compared with advanced diagnostic blood tests and cardiac imaging modalities which require enormous capital expenditures (i.e., cardiac cath lab, nuclear stress camera) and highly trained professionals with years of experience.

One of the most interesting patients was the patient who suffered the acute myocardial infarction post-operatively. The patient was exhibiting no anginal symptoms yet the pre-op PlainSight score was significantly abnormal (>60). Risk stratification of patients pre-operatively is a current weakness in cardiovascular assessment and could be greatly aided by a simple noninvasive test. If the

PlainSight score could be validated for the pre-operative risk assessment for non-cardiac surgery, the economic and medical benefits to the health system and patients would be immense.

The PlainSight algorithm may also be useful in the risk assessment and triage of patients in the medical office and emergency department setting. Patients who present with chest pain could be more rapidly evaluated using the PlainSight algorithm rather than even the currently available rapid troponin assay. Furthermore, given its strong PPV, appropriate patients with abnormal PlainSight scores may be eligible for a "fast-track" invasive evaluation, saving ED time and resources.

From a global health perspective, the PlainSight algorithm has the potential to screen various cardiovascular conditions using an inexpensive, completely noninvasive test which most importantly, does not require expert interpretation. Its potential value in rural/underdeveloped/underserved areas without local access to advanced cardiovascular care cannot be over-stated.

As the technology is refined, PlainSight is adaptable for use by the lay public using 4 simple limb lead electrodes and a smartphone app. A simple numeric score is readily understandable by the public at large. Furthermore, even in well developed countries with advanced medical care, the use of PlainSight by the general population may enhance patient compliance, improve early detection and potentially lower overall diagnostic testing.

Given its ease of use, zero complication risk and straightforward software-based implementation, the PlainSight algorithm may be suitable to add on to every single diagnostic ECG performed and even during continuous ECG monitoring environments. The simplicity inherent to PlainSight also lends itself readily to telehealth applications further broadening its potential scope of usage. Based upon the data collected to date, potential applications of the PlainSight algorithm include:

1) General population screening for cardiovascular health
2) Use in non-cardiovascular specialist medical settings for consideration of referral to a cardiovascular specialist
    a. Primary care offices
    b. Pre-operative screening
3) Continuous monitoring during intra-operative procedures to monitor for cardiovascular abnormalities

4) Use in the Emergency Departments for the triage and evaluation of patients with a broad range of cardiovascular disease
5) Use by cardiovascular specialists to further risk stratify patients with known or suspected cardiovascular disease
6) Use of PlainSight as adjunctive analysis during routine (or simplified) stress testing without advanced cardiovascular imaging

PlainSight did "miss" several cases of non-ST elevation myocardial infarction (NSTEMI) or significant symptomatic coronary artery disease (e.g., 6/23 troponin + patients were missed by PlainSight in this study). The retrospective nature of this study may have affected results (e.g., timing of ECG acquisition vs collection of blood samples).

PlainSight offered variable ability to analyze patients with LBBB and/or ventricular paced rhythms. In general, patients with LBBB or ventricular paced rhythms have extremely difficult to interpret ECG's. They are typically nondiagnostic except in the most extreme situations. Many more additional patients with LBBB or ventricular paced rhythms will require analysis to determine if PlainSight is useful in this challenging patient population.

Finally, the PlainSight technology offers potential additional insight into cardiac physiology other than a simple numeric score. The algorithm is designed to offer spatial localization as well as color coded severity. This study was specifically designed to assess the utility of the basic PlainSight functionality; future prospective studies will be necessary to further characterize all of the technology and its optimal use.

In summary, PlainSight performed remarkably well in this pilot study. An overall sensitivity of 76% coupled with a specificity of 88% used in a broad spectrum of cardiovascular disease is a promising finding – especially when compared against the most advanced cardiovascular testing we have available in 2021. Future prospective studies should focus on the proposed application areas to determine if PlainSight can deliver on these preliminary results.

References

[1] Fye WB. A history of the origin, evolution, and impact of electrocardiography. Am J Cardiol. 1994;73(13):937–49.

[2] Wilson FN, Kossmann CE, Burch GE, Goldberger E, Graybiel A, Hecht HH, et al. Recommendations for standardization of electrocardiographic and vectorcardiographic leads. Circulation. 1954;10(4):564–73.

Submitted,

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Appendix A PlainSight Algorithm

Every time a muscle contracts, fluctuations in electrical voltage occur which initiate the mechanical contraction of the muscle – whether it is the bicep or the heart. The electrocardiogram detects minute changes in the electrical charge on the skin generated by the heart. A "six-lead" ECG signal is taken using four electrodes (one each on a subject's wrists and ankles). It can be performed quickly and non-invasively on a fully clothed patient who is either seated or lying on their back. PlainSight was designed to analyze signals from a six-lead ECG. PlainSight requires only 30 seconds of data for a thorough analysis and thus a comprehensive cardiac screening can be performed accurately in as little as three minutes by anyone with minimal training on the device, including home users.

Furthermore, PlainSight is a software solution which can be applied to ECG signals captured with any digital ECG recording device capable of capturing the voltages from limb leads at a rate of 500 samples per second including six lead, 12 lead and other variations of electrode placement. It can be used for real time analysis or for the further analysis of signals captured years ago.

PlainSight embodies a patented method of ECG signal analysis termed Amplitude Variability Analysis (AVA). The simplest explanation of AVA is that it uses the power of computer analysis to reveal patterns of heart dysfunction that are measurable and repeatable but invisible to traditional interpretations which are based on what the human eye can see and what the human mind can process from waveforms rendered on graph paper.

The idea behind the technique is that many "sudden" cardiac events do not happen all that suddenly; we just miss the warning signs. By analyzing thousands of digitized EKG signals, the developers discovered various levels of cardiac distress will produce a proportionate degree of "rumbling" in an EKG signal. This rumbling can be represented visually as tiny waves within the larger waves of an EKG readout. Where one would expect to see a smooth and regular curve, minute fluctuations in the signal occur which indicate portions of the heart muscle are not producing the intensity of electrical signal expected while other sections may be working harder to make up for the difference.

Using rapid computer analysis, a 30 second acquisition can be analyzed so each individual heartbeat can be isolated and analyzed in comparison to other beats occurring in that timeframe. PlainSight can then calculate the frequency, intensity and variability of those fluctuations and quantify them as a numeric value (a deviation score) which has been shown to have great predictive value for hidden

cardiac disease. Because the EKG signal is a linear plot and the progression of a heartbeat follows a linear sequence of contraction and relaxation, those deviation scores may be mapped to individual parts of the organ for an even higher degree of specificity.

The combination of traditional analysis techniques and EKG Insights' unique AVA provides a rich set of data that can be incredibly useful to researchers and clinicians but that data still remains beyond the understanding of anyone who has not been trained in the formal analysis of ECG signals or the range of pathologies that can impact heart health. PlainSight makes a huge leap in opening that data up to the average person by rendering the entire data set produced by the algorithm in a single, powerful and intuitive visualization that presents a model of the human heart shaded according to the location and intensity of anomalies uncovered during the analysis.

This model is divided into fifteen regions and incorporates data from pulse, rhythm analysis and AVA indices which are then translated into a color-coded portrait of overall heart health. In this model, a normal interpretation would be a uniform green. Any suspected problem areas related to the AVA would manifest as shades of red with the intensity and size of the shading areas increasing relative to the intensity of the amplitude variability in the associated region of the ECG signal. Rhythm disorders manifest as shades of blue. When multiple adverse findings converge (pulse, rhythm, traditional PQRST measurements outside of normal range), additional indicators of intensity (pattern variation as well as color) communicate the severity of the combined factors. The utility of the overall "score" as well as the more detailed "mapping" remains to be clinically validated.

Appendix B Raw Data

EKG File	EKG reading	Diagnosis	COVID	Trop	Diagnostic Findings	PlainSight Score
2	IVCD	NSTEMI	-	+	ramus PCI	71
4	IVCD	NSTEMI	-	-	after PCI	35
5	RVR, TWI	AF RVR, PE	-	-	normal echo 2017	40
6	RBBB, LAFB	subacute MR, mod AS	-	-	sev MR, sev PH	40
7	NL	remote IMI , stable CAD	-	-	stable CAD	16
9	ST, LV	large PE	+	-	large PE, CT RV strain, neg echo	35
10	ST, NSSTTWA	PE	+	+	emboli shower, CT RV strain	18
11	LAFB	COVID, sepsis	+	+	? Type II NSTEMI	44
12	ST	hypoxia	+	-	norm T	17
13	IVCD	sepsis	+	+	abn T	48
14	ST	ARDS/CM	+	-	neg T ; CM on echo	16
16	normal	PNA/aortic thrombi	+	-	PNA	12
17	ant Q	fever/CKD	+	-	cardiomyopathy	26
18	ST	COVID PNA	+	-	neg T	19
19	NSSTTWA	COVID PNA/SICM	+	+	abn T ; CM on echo	50
20	AF, NSSTTWA	COVID PNA/shock	+	+	Abn T	52
21	Low voltage	prothrombotic	+	-	neg T	19
22	ST	pregnant	+	-	neg T	20
23	SB, LVH	resp failure	+	-	BNP	15
24	NSSTTWA	SOB	+	-	PNA	14
25	STE V3-V4	PNA	+	-	PNA	15
27	NSSSTWA	resp failure	+	-	PNA	25
28	ST	SICM	+	+	takotsubo	18
29	NSSTTWA	CAD, pre-op screen failure, baseline	-	-	1 year prior	19
30	NSSTTWA	CAD, pre-op screen failure, pre-surgery	-	-	pre-surgery	64
31	NSSTTWA	CAD, pre-op screen failure, NSTEMI	-	+	LAD PCI, RCA FFR normal	35
32	twi	CAD, pre-op screen failure, post PCI	-	-	TWI	29
33	normal	cor calcium, normal perfusion	-	-	no sig CAD	15
35	NER	syncope	-	-	normal echo	16
36	inf QW	angina, abn stresA	-	-	grafts to OM1 and OM2 PCI ; RCA old IMI	15
37	ant Q, inf STD	Onc, checkpoint	-	+	nop LAD, EF 35%	29
38	TWI	NSTEMI	-	+	mid LAD PCI	24
39	ant TWI	severe AS by echo	-	-	mild AS by cath	15
40	SB	COVID PNA	+	-	PNA	14
43	TWI V1-V2	PPH	-	-	severe PH, RVE	38
45	STE AVR	OHCA, PEA		-	cardiac arrest	36
46	NSSTTWA	NSTEMI	-	+	occluded distal RCA	21
47	NSSTTWA	NSTEMI	-	+	severe prox LAD	16
48	LAFB	AS	-	-	FFR neg LAD, AS	26
49	Normal	abn stress test	-	-	abn stress, neg cath	15

50	low voltage, ST	tamponade	-	-	tamponade	35
51	LBBB	stable angina	-	-	RCA dissection (old)	70
53	PRWP, PVC	NSTEMI	-	+	ICM, 3VD	39
54	RBBB	abn stress test	-	-	abn stress, 3VD	19
55	IVCD	HOCM	-	-	HOCM	62
56	normal	abn stress test	-	-	abn stress, 3VD	19
57	NSSTTWA	abn PET stress	-	-	abn PET stress, neg cath	19
58	AF, RBBB	NSTEMI	-	+	severe CFX	39
59	AF, NSSS	AS, CAD	-	-	severe AS	14
60	SR, PAC, NSSTTWA	abn SE	-	-	abn SE, 3VD	47
61	old IMI, ASM	ICM	-	-	severe ICM	38
62	ASMI	ICM	-	+	ICM, 3VD	18
63	SB, LVH	abn stress test	-	-	mod LAD, severe RCA	15
64	TWI	NSTEMI	-	+	2VD	22
65	ST	PPH	-	-	PPH	14
66	Paced rhythm	stress with apical scar	-	-	abn stress, neg cath	61
67	normal	abn SE	-	-	abn SE, neg cath	15
68	normal	COVID	+	-	MILD HYPOXIA	12
69	RBBB	COVID/sepsis	+	+	ARDS, SEPSIS	38
70	biV paced	severe ICM	-	-	severe ICM	23
71	ST depression	NSTEMI	-	+	3VD	35
72	low voltage	tamponade	-	-	tamponade	39
74	LVH, strain	psychosis	-	-	normal echo	21
75	ant Q waves, LVH	HOCM	-	-	HOCM	26
76	NSSTTWA	CAD s/p CABG	-	-	patent grafts	27
77	LV, atrial bigeminy	CAD	-	-	CTO LAD, NL LVEF	38
78	normal	abn stress test	-	-	neg cath	16
79	nsstwa	DCM	-	-	severe NICM	15
80	a paced, NSSTTWA	ICM	-	-	severe ICM	40
81	NSSSTWA	HIV, COVID, ARDS, PNS	+	-	ARDS	16
82	NSSSTWA	COVID, aortic thrombi	+	-	aortic thrombi	12
84	NSSSTWA	COVID PNA	+	-	PNA	41
85	RBBB	AS	-	-	AS pre-TAVR	24
86	NSSSTTWA	severe MR, endocarditis	-	-	severe MR	22
87	Normal	Class II angina, moder LAD	-	-	mod LAD, PCI	14
88	ST dep V4-V6	severe HFpEF, CAD s/p CABG	-	+	sev acDHF, stable CAD	44
89	LVH strain	stable CAD, abn stress	-	-	stable CAD, abn sterss	26
90	SB, LVH	NSTEMI, unclear culprit	-	+	no clear culprit for NSTEJI	27
91	ant QW	AS, CAD	-	-	mod AS, severe mid LAD	24
93	LV	cSHF, LVEF 35%	-	-	acute HF, severe PH	35
94	LVH	abn ECG, pre-renal tx	-	-	no CAD	20
95	PRWP	NSTEMI, ? Myocarditis	-	+	NSTEMI, no culprit	18
96	diffuse TWI	NSTEMI	-	+	3VD	18
97	inf STE	STE wihtout culprit,	-	+	normal LV, MINOCA	20
99	NSSTTWA	mild MR	-	-	mild MR	15

100	NSSTTWA	remote NSTEMI, PCI	-	-	stable CAD, remote PCI	15
101	normal	BAV with mod AI	-	-	stable BAV mod AI	15
102	NSSSTWA	pre-op vasc ; multiple CRF	-	-	normal stress test	15
103	normal	Atypical chest pain	-	-	normal stress	15
104	LV, NSSSTWA	Atypical chest pain	-	-	normal PET	18