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Cost Effective Coronary Care – A Novel CAD Assessment Protocol

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ABSTRACT

According to the Centers for Disease Control and Prevention, heart disease is the number one killer in America today. Nearly 2,400 people die each day from heart and blood vessel diseases and more than 7 million Americans have suffered a heart attack in their life time, according to American Heart Association data. Around 500,000 of these individuals will experience recurrence in a year. More than two million patients are triaged and treated for acute coronary syndrome in emergency wards across the country each year. These statistics are increasing by the day. A significant amount of research has therefore been devoted to screening for coronary artery disease (CAD) and to the delineation of mild and moderate from significant CAD disease. Despite the expensive and elaborate testing modalities that are being utilized, the incidence of sudden coronary events and cardiac death is still the leading cause of mortality and disability in the US. Therefore, coronary angiography is still the gold standard to identify significant CAD. With increased coronary angiography, there is increased coronary angioplasty. Hence, CAD is also the number one offender of healthcare spending. Unfortunately, despite the extensive investment in high cost modalities for differentiating mild to moderate CAD from significant CAD, no clear confidence has been instilled in cardiologists to safely avoid unnecessary catheterizations and coronary angioplasties. Hence, the need exists for a cost effective, reliable, non-invasive and universally easy to use modality to differentiate mild to moderate CAD from significant CAD. In this manuscript, we introduce a novel noninvasive coronary ischemia screening and CAD evaluation protocol using the CS-100 (Cardio Scan–100) Frequency Cardiograph (FCG) analysis system.

Keywords: CAD, Acute coronary syndrome, Coronary care, Cardio Scan–100

BACKGROUND

Acute coronary syndrome (ACS) is the umbrella term for clinical presentations of different stages of myocardial ischemia, ranging from angina/unstable angina (USA) with mild to moderate coronary artery disease (CAD) to acute ST-segment elevation myocardial Infarction (STEMI). Coronary Artery Disease (CAD) with plaque build-up in the coronary arteries compromises myocardial blood flow and modifies myocardial compliance, contractility, and blood flow dynamics. Coronary insufficiency can be from mechanical obstruction due to plaque build-up or from abnormal vasoreactivity due to vascular endothelial cell dysfunction and vascular inflammation. Abnormal vascular wall homeostasis with low vascular wall nitric oxide concentration and increased free radical (reactive oxygen species-ROS) pool occurs from dysautonomia-induced endothelial cell dysfunction. These are dynamic modifications that can be difficult to quantify. Abundant laboratory evidence indicates that inflammation plays a major role in all stages of atherosclerosis. Clinical evidence from several prospective studies demonstrates that inflammatory biomarkers independently predict vascular disease risk with a magnitude of effects as significant as increased blood pressure or high cholesterol. Prospective analysis from JUPITOR trial data indicate that achieving low levels of inflammation may be as important as achieving low levels of LDL-c cholesterol [1]. JUPITOR data prospectively confirms data from several prior studies including CARE, AFCAPS/TexCAPS, PROVE IT, TIMI22, A to Z, REVERSAL. These trials corroborate laboratory evidence that anti-inflammatory processes reduce cell adhesion, monocyte recruitment at the arterial wall, augmented expression of the transcription factor KLF2 with consequent migration of inflammatory and thrombotic mediators, altered smooth muscle migration and reduction in IL-6 and other cytokines triggering plaque development.

Extensive research and a plethora of non-invasive testing modalities such as nuclear stress testing with Dobutamine

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Stress ECHO (DSE), SPEC imaging, pharmacologic stress testing with imaging, positron emission tomography (PET) imaging, coronary computed tomography angiography (CCTA) and coronary calcium scoring are some of the newer modalities that are being investigated to assess CAD and delineate mild to moderate CAD from significant CAD. This differentiation has both prognostic and therapeutic value. While significant CAD has a strong correlation to mortality and morbidity, mild to moderate CAD has good long-term prognosis with medical management alone. Fear of missing the monster (significant CAD) has driven research and the cost of caring for patients with CAD. Unfortunately, despite the extensive investment in high cost modalities for differentiating mild to moderate CAD from significant CAD, no clear confidence has been instilled in cardiologists to safely avoid unnecessary catheterizations and coronary angioplasties. This has been clearly demonstrated in the recent National Cardiovascular Registry (NCDR) data. Retrospective NCDR registry analysis of >400,000 positive non-invasive coronary ischemia tests found obstructive CAD association in only 38% overall [2]. In female patients, particularly, only 33% had obstructive CAD, while >55% had normal angiograms. Appropriate use criteria (AUC) and unnecessary angioplasty recommendations generated by ACC and AHA, based on NCDR registry findings, have been arguably debated by interventionists for lack of high specificity and sensitivity in the available modalities to delineate false positivity and prevent false negative results. This forces interventional cardiologists to err on the side of safety. Hence, the need exists for a cost effective, reliable, non-invasive and universally easy to use modality to differentiate mild to moderate CAD from significant CAD.

Recent NCDR registry 2010 data analysis by Patel et al. [2] demonstrated poor yield from non-invasive testing in identifying significant CAD by coronary angiography and identified coronary angiography as the culprit for wasted healthcare dollars and demonstrated poor health care delivery. The American Heart Association (AHA) and the American College of Cardiology (ACC) therefore updated practice guidelines and performance measures for CAD to help clinicians adhere to standard of care. Appropriate use criteria (AUC) were developed by a task force from ACC to limit overuse of angiography and revascularization procedures. This was prompted due to recent literature demonstrating comparable mortality and morbidity between aggressive medical management and coronary revascularization. The cost for revascularization has skyrocketed in the last three decades. Despite the widespread use of percutaneous coronary interventions (PCI), the appropriateness of these procedures in contemporary practice is unknown and the mortality from CAD has not been affected by PCI. Based on this premise, there was a recent prospective study conducted to evaluate appropriateness of PCI highlighting inappropriate use of PCI [3-5]. However, stakes are high in ACS in high-risk groups to not intervene with PCI and adapt medical management safely. An expert panel published a study recently offering constructive criticism of the AUC and pointed out the deficiencies in AUC and the risk involved in adapting the AUC in high risk groups (Percutaneous coronary intervention uses in the United States: Defining Measures of Appropriateness by Arbab-Zadeh et al. [4]. They argued that while minimizing overuse of PCI is important, the AUC that were developed do not assess properly the effectiveness of PCI in high risk subgroups such as DM-II, known as significant CAD. In their criticism, they highlighted a few facts and made recommendations for revisions to AUC [6]:

- Relying on these tests for authorization for coronary angiography would be inappropriate.
- Provocative testing in high-risk symptomatic patients is risky.
- Minimizing overuse and underuse of PCI should be a national healthcare priority.
- The AUC do not assess effectiveness (PCI can be appropriate without improvement of symptoms).
- Scenario 12B (1- or 2-vessel disease, without proximal LAD, low-risk findings on noninvasive testing, 0 or 1 anti-angina medications (of CCS class I or II) should be changed to 'uncertain.'
- The CTO-specific AUC categories should be removed.

The above concerns by experts highlight the unpredictability of CAD and the inadequacy of current noninvasive testing in assessing obstructive CAD (OCAD). This is more so in high-risk groups such as women and diabetics. Various types of testing modalities for coronary ischemia are recognized as sensitive but lack specificity with high false positivity. There is growing consensus that this lack of specificity results in a significant number of unnecessary coronary angiographies thereby exposing patients to risk of invasive procedures without commensurate clinical benefit. Patel et al published an analysis of the ACC-NCDR of patients undergoing coronary angiography, which included 397,954 patients. CAD was absent in 39.2% of patients. The authors created four separate models for predicting positive results on angiography: 1) Framingham risk score alone; 2) Framingham score plus clinical risk factors; 3) Framingham score, clinical risk factors and presence of symptoms; and 4) results of non-invasive testing (i.e., stress testing). The pre-test predictability of significant OCAD after clinical presentation was 0.67 in this study. Adding Framingham scoring improved the positive predictability to 0.74. Additional non-invasive testing improved the positive predictability to only 0.76 for a significant increase in the cost of care that is not justified.

In patients presenting with ACS, the presence of 2 or more Framingham risk factors, diabetes and female gender

predisposes to higher mortality. Sudden cardiac death is the first presentation of CAD in up to 52% of women. Silent myocardial ischemia and silent infarctions are common in diabetics and women. Among patients with known previous CAD, the occurrence of false positive test leading to unnecessary catheterization and false negative test resulting in costly miss of significant OCAD is high, particularly in diabetics and women, as demonstrated in the Patel et al.'s NCDR analysis [2]. We have also found up to 49% discordance in a retrospective analysis of three years of catheterization lab census between stress test results and findings at coronary angiography in patients undergoing coronary angiography based on noninvasive testing at our institution. Therefore, using AUC to guide therapy and relying on noninvasive testing with poor yield and specificity is not prudent. We believe these findings in diabetics and women are due to abnormal vasoreactivity paradoxical vasoconstriction to acetylcholine stimulation (can be tested by brachial artery reactivity testing (BART)) from endothelial cell dysfunction and vascular inflammation. Provocative testing such as exercise stress testing and pharmacologic stress testing in these patients is unreliable and can induce vasospasm that results in false positive tests. At RENU-CA research we have extensively demonstrated dysautonomia and abnormal vasoreactivity clinically over the last 12 years in >1000 patients. Framingham risk scoring system for 10 year coronary heart disease prediction has been developed based on which patients can be categorized into mild, moderate and high-risk groups. This is standard of care practice and has stood the test of time by the cardiology community. National cholesterol education program (NCEP) and American Heart Association guidelines now recommend presence of Diabetes Mellitus to be considered as known independent CAD risk. Dysautonomia is a common association in type-II diabetes and women; hence there is a higher incidence of abnormal vasoreactivity. Patel study therefore demonstrated lower yield in Women and diabetics with high false positivity. Also, these sub-groups of patients have a higher predisposition to acute coronary events therefore are independent risk factors [7].

COMPUTERIZED CORONARY TOMOGRAPHY ANGIOGRAPHY

Due to poor yield in delineating OCAD by noninvasive testing, newer modalities of testing have been developed. Computerized coronary tomography angiography (CCTA) is a newer modality for CAD assessment. In a recent publication, researchers used Medicare administrative data analysis and found that patients undergoing CCTA were more likely to undergo subsequent confirmatory coronary angiography and revascularization relative to those receiving traditional stress testing thereby, increasing the cost of care [8-12]. Yet despite this increased cost from utilization of resources, the short-term outcomes were similar. The CORE-64 (Coronary Artery Evaluation using 64-Row Multi-Detector Computed Tomography Angiography) International Multicenter Study published recently concluded that both pre-test probability for CAD and coronary calcium scoring should be considered before using CTA for excluding OCAD [13-19]. This study highlighted the inadequacies of CTA and its lack of efficacy in patients with calcium scores of >600 and in patients with a high pre-test probability of OCAD. The negative predictive value of CTA dropped from 0.93 to 0.50 in patients with known CAD and 0.93 to 0.75 in patients with calcium score of <100 [5]. Based on these findings, CTA is not recommended for diagnostic purposes in patients with substantial coronary calcification and in very low coronary calcification. CTA is also unreliable in high-risk groups with known prior CAD. CTA is also an anatomic marker of CAD and does not indicate functional significance. In determining the use of coronary CTA, one needs to also consider the potential harmful effects of radiation. The doses of radiation needed are substantial, 12-15Sv, equivalent to 600-800 chest X-rays or 3-7 coronary catheterizations. This may predispose to malignancy notwithstanding the expense of performing CTA. CTA also has exclusion criteria such as serum creatinine >1.5 mg/dl, prior cardiac surgery, Class-III/IV heart failure and atrial fibrillation, recent coronary intervention within 6 months, intolerance to beta-blockers and BMI>40 kg/m^2 BSA. In summary, newer testing modalities for CAD assessment are expensive, cumbersome with minimal yield or added benefit to patient care. A recent comparison study of Coronary CT Angiography, SPECT, PET and Hybrid imaging for diagnosis of Ischemic Heart Disease Determined by Fractional Flow Reserve (FFR) from the Netherlands was published in JAMA Cardiology fall 2017. Their conclusion in this head-to-head comparison in 208 patients is PET scan exhibits the highest accuracy and FFR did not add incremental diagnostic yield [18].

Percutaneous coronary intervention and Visual-Functional mismatch

With over use of coronary angiography comes the problem of over use of PCI. In a multi-center trial of patients within the NCDR undergoing PCI during the period of July 2009-September 2010 in 1091 hospitals in the US, Chan et al. addressed appropriateness of PCI [2]. In this multi-center study, the appropriateness of PCI was adjudicated using AUC developed by ACC. Results were stratified by whether the procedure was performed for an acute (STEMI or non-STEMI or high-risk USA) or non-acute indication. Over 500,000 PCIs were evaluated. In this large contemporary cohort, nearly all PCIs were appropriate in the acute situation. In the non-acute cohort, however 12% PCI's were classified as inappropriate with significant inter-hospital variability. This study has obviously created a controversy in interventional cardiology, particularly because the NCDR data collection forms have quite a few shortcomings in being truly representative of real world scenarios and AUC criteria are not optimal. Nevertheless, it raises an issue with the appropriateness of elective PCIs. Several investigators have

reported discrepancies between the severity of coronary angiographic stenosis and the functional severity – the so-called Visual-Functional mismatch. In one study of 143 patients with angiographic 3-vessel disease, 77 (54%) had no perfusion defects or only 1-vessel pattern as determined by perfusion imaging [19]. In another study of 67 patients with angiographic multi-vessel disease, 26 patients had no perfusion defects and 24 had only 1-vessel perfusion defect according to myocardial perfusion imaging performed after coronary angiography [20]. The fractional flow reserve versus angiography for multi-vessel evaluation (FAME) study published recently is a landmark study exposing the Visual-Functional mismatch phenomenon. A recently published sub-analysis of the FAME study thoroughly evaluated the Visual-Functional mismatch phenomenon of CAD [21]. Of the patients with 3-vessel disease as assessed by visual estimation, only 14% had 3-vessel disease after FFR (Fractional Flow Reserve) measurement, whereas 9% had no functionally significant stenosis. These findings indicate that in the absence of FFR, approximately 40% of the PCIs would have been performed in functionally insignificant stenotic lesions. Furthermore, a significant number of so called 3-vessel disease patients sent for bypass surgery can be treated by PCI. This phenomenon of Visual-Functional mismatch occurs due to multiple factors. These include lesion factors such as lesion length, eccentricity, size of the vessel and the amount of myocardium in jeopardy. A moderate stenosis in a vessel that supplies large myocardial territory can be functionally significant; whereas, a significant stenosis in a small vessel with minimal myocardium at risk may not be functionally significant. This is a mathematically driven phenomenon; therefore, FFR is very sensitive in this situation. Perfusion imaging may not be able to differentiate subtle ischemic burden from significant ischemia functionally.

When dealing with CAD, which can become life threatening rapidly, one of the concerns among physicians is the long-term safety of differing invasive treatment. Nuclear imaging studies have suggested that treatment of non-ischemic coronary lesions may be different, but safe [22]. In a meta-analysis of thallium single photon emission computed tomography (SPECT), the annual incidence of death or myocardial infarction was less than 1% per year in these patients. Patients with lesions with insignificant FFR values were also shown to have favorable outcomes [23,24]. A randomized trial to address this concern is the DEFER study (FFR to Determine Appropriateness of Angioplasty in Moderate Coronary Stenosis). In this study, 5 year outcomes in patients were randomized to medical therapy vs. PCI based on FFR<0.75 or >0.75 for death or myocardial infarction was <1% [25]. In response to these findings, there is a big push in interventional cardiology for using intravascular ultrasound (IVUS) and FFR in guiding PCI. Recently published results of the FAME study demonstrated that patient and lesion selection and treatment decisions based on systematic assessment of FFR may improve clinical outcomes of PCI and save costs as well, particularly in the multi-vessel disease due to limiting unnecessary PCIs [26]. Because of the data from this pivotal trial, the results have been incorporated into the current guidelines for patients with CAD. United States PCI guidelines now have classification of recommendation class-IIa for FFR with a level of evidence A. European PCI guidelines have also adopted FFR. FFR is unique and preferred in the accurate assessment of functional significance of stenosis of individual coronary artery because FFR has a sound mathematical basis that has been validated extensively. Adding routine use of FFR and IVUS during all PCI procedures, however, becomes a cost issue and to some degree a safety issue as well. FFR and IVUS are also assessments during angiography and may have some limitations in some patients such as those with diffuse distal disease, where FFR may over estimate and in tortuous vessels where FFR and IVUS may not be feasible. Since it is an assessment done during angiography, there may be an element of bias in committing to PCI due to the effort and time involvement by the operator to arrive at a conclusion that may favor PCI. In a recent analysis of 661,063 patients undergoing coronary angiography for abnormal noninvasive coronary ischemia evaluation including single photon emission computed tomography-myocardial perfusion image (SPECT-MPI) and CCTA, out of 81% with abnormal studies prior to angiography only 45% had significant obstructive CAD>50% [27].

Therefore, noninvasive FFR assessment modality is under investigation and studies have been published evaluating the usefulness and accuracy of noninvasive FFR assessment derived from CT angiography as shown in a recent report [28]. In these studies, the efficacy and usefulness of non-invasive assessment of functional coronary stenosis has been demonstrated to be comparable to invasive FFR. FFR derived from CCTA images (FFRct) is emerging as a novel non-invasive method to evaluate lesion-specific diagnosis of CAD. CT-derived FFR is calculated by processing the same images used for evaluating coronary arteries under resting conditions. The significance of coronary lesions at hyperemic flow condition can be estimated by computational flow modeling, and no adenosine is required. Thus, CT-derived FFR estimates virtual hyperemia for the calculation. Hence, additional image acquisition, radiation exposure, or pharmacological stress during CCTA scanning, are not necessary for the computation of FFR from coronary CT. Based on the recent FFRct data the Centers for Medicare and Medicaid Services (CMS) will begin reimbursing for the HeartFlow FFRCT Analysis under a New Technology Ambulatory Payment Classification (APC). The reimbursement will be $1,450.50 for the technical component of the test. A HeartFlow-guided strategy reduced the overall costs to the healthcare system by more than $4,000 per patient after one year. The mean one-year per-

patient cost for the usual care strategy was $12,145 compared to the $8,127 cost for the HeartFlow-guided strategy. When including the $1,500 cost of the HeartFlow Analysis, the cost reduction is 26% [28-36].

Although numerous studies have shown the prognostic value of anatomical stenosis by CCTA [37,38], this misclassification may influence the treatment decision making among patients with suspected CAD and future risks. In a study of 81 patients who underwent both ICA with FFR and CCTA, when invasive FFR ≤ 0.75 was considered appropriate for revascularization decision making, 30% of patients failed to undergo appropriate revascularization by CCTA guidance due to lack of evidence of functional significance or inappropriate deferral compared to FFR guidance [39]. Thus, based on these issues, we may need a new approach after CCTA performance to more accurately identify patients who would benefit from revascularization.

From all the above data and studies, it is clear that the problem of delineating mild/moderate CAD from significant CAD is an unresolved issue. Furthermore, most modalities that have been developed are prohibitively expensive and cumbersome, with limited access to most patients and the community at large. In this era of cost containment in medicine, appropriate diagnosis and treatment of CAD is a difficult task as the price of missing significant disease among all comers can be mortality and high morbidity from heart attacks.

OVERVIEW OF THE MULTIFUNCTION CARDIOGRAM (MCG)/FCG-CS100 ANALYSIS

New non-invasive modalities that electronically deconstruct cardio-electrical current data from multiple lead electrodes over 70-90 s of continuous monitoring by complex multi-step mathematical transformational analysis into functional components called indexes. This information is then digitized using standard Fast Fourier Transformation (FFT) analysis. This electrical information from the heart reflects the dynamic interaction of the myocardium and intra-cardiac blood flow over multiple cardiac cycles. The data is then compiled into indexes that are compared against >20,000 validated database of patients with known heart disease and normal people to develop cohesive patterns that allow rapid computerized pattern recognition. Two different operating systems based on the same analysis model and validated database have been developed: MCG and FCG-CS100 systems.

The Multifunction Cardiogram also referred to as the 3DMP and FCG-CS100 analysis is a completely new approach to diagnosing cardiac disease that uses complex mathematical analysis and are the first examples of tools in the discipline of "Clinical Computational Electrophysiology". They use mathematical analysis of resting electrical signals from the heart to aid in detecting CAD and thus improve patient selection for angiography and PCI. This has significant prognostic value and is cost effective as well.

MCG uses systems analysis approach in obtaining an objective and quantitative assessment of CAD. It uses six mathematical transformations to study cardiac electrical signals. These transformations enable detection and analysis of changes to the electromyocardial physiologic function that result from alterations in coronary blood flow. Instead of merely retrieving summed information about the electrical activity of cardio-myocytes at a single time point during a single cardiac cycle, as a traditional ECG does, MCG/CS-100 are specifically engineered to collect data over an 82 s period synchronously from only two leads, thereby obtaining information about the dynamic interaction of the myocardium and intracardiac blood flow over multiple complete cardiac cycles. MCG digitizes the individual's electrical signals, deconstructs them via the six mathematical transformations into multiple functional components (called indices) and then reconstructs them by mathematically integrating the indices into a cohesive pattern that allows rapid computerized pattern recognition. This deconstruction and re-synthesis of the information extracted from these multiple functions allows one to study the interactions between the information obtained from each lead, which is impossible using conventional 12 lead ECG. By comparing the individual's pattern to other patterns contained in a large database, it is possible to model, quantify and understand the ongoing stress-strain interaction between the myocardium and intracardiac blood flow, which enables one to directly and objectively identify chronic (Hibernating myocardium) or acute coronary ischemic alterations. Therefore, MCG is a comprehensive ischemia and myocardial function test that can be used for identifying various levels of functional myocardial ischemia and for identifying hibernating myocardium. CS-100 analysis also operates on the same principles.

It is important to emphasize that both the analytic approach and the information in the database have been validated. First the indices and patterns obtained from the mathematical transformations have been empirically derived as well as verified and validated to be clinically meaningful. Second, all the patient data entered into the database, against which an individual's patterns are compared for the purposes of obtaining diagnostic information, has also been validated and verified. The index cluster and pattern for each patient's data has been correlated with the findings of coronary angiography, other relevant diagnostic work-up and the final diagnosis of the treating physician, which has been verified by at least two independent expert diagnosticians in the field. As information in the database accumulated, additional requisite internal validation, internal to the engineering process, was performed. After these validation procedures were completed and the system's final iteration met the intended purpose of the original design, external peer review quality clinical validation trials of the entire system were

carried out (i.e., published MCG clinical trials). MCG has been cleared by the FDA as an aid to diagnosis by means of analysis of ECG waveforms in the frequency domain (power spectral estimate). FCG-CS100 system is also based on the same system analysis as MCG but utilizes cardio-electrical data generated from 2-lead electrodes as well as 12 leads electrodes thereby allowing localization of stenosis specific to individual coronary artery affected.

CS-100 TESTING

Multiple cycles of complete resting ECG analog signals from 12 leads are recorded by a portable Laptop device from a patient at the point of care over duration of 80-90 s.

Digitization, encryption, Fast Fourier Transformation of the raw data and mathematical transformations of the data and their comparison to database is all built into the system unit at the point of care. The data is then compiled and a total of 113 indexes (60 indexes @5/lead from 12 leads and 53 indexes from 2 leads) are compared against the same 27,000 empirical databases as used by the MCG system. This database consists of 27,000 people with CAD, whose CAD status and severity is included in the database and has been confirmed by coronary angiography. Importantly, database also contains MCG/CS-100 results from many patients who have one or more non-ischemic cardiac diseases. Therefore, the database is used to distinguish patterns in patients with cardiac ischemia and non-ischemic cardiac disease(s). Approximately 13,000 of the patients in the database have had normal coronary angiograms or have been determined to not have CAD after independent evaluations by two cardiologists. The database has been carefully accumulated over many years, and the patterns of each entrant have been validated and correlated with the presence (or absence) and severity of CAD. The database has been designed to be robust and to minimize bias by including, among other things, 49% of its data from women and an age range of 14-100 in the CAD and non-CAD groups, as well as people with many forms of heart disease (e.g. arrhythmias, hypertrophy, cardiomyopathy), in addition to CAD. The database also contains other clinical and diagnostic data from all 40,000+ patients, including information about other non-cardiac disease entities.

MCG data has been used to predict the findings of coronary angiography in several carefully designed and well-conducted prospective double-blind validation clinical trials in seven countries [28-32]. In these studies, MCG was performed on patients who were scheduled for elective coronary angiography based on clinical impression and standard non-invasive testing, with a belief that the patients had an intermediate to high risk of having relevant coronary artery stenosis (CAS) defined as 70% or greater in one or more epicardial coronary arteries or 50% stenosis of the Left Main artery. These studies have some bias in the sense that these were patients who were committed to angiography prior to MCG testing. In our early experience with MCG we did encounter some false positive tests particularly in women and diabetics both of who are vulnerable groups for silent untoward coronary events. MCG system also lacks specific coronary artery localization capability which can be a shortcoming in its application for known CAD patients for follow up monitoring and lesion severity assessment post angiography. CS100 system is a more elaborate and coronary artery specific analysis with the same underlying principles as MCG. CS100 system analyzes 12 leads and 2 lead electrical inputs and therefore has the capability to delineate specific coronary artery territory and can give lesion specific information in the assessment of known CAD patients. This capability of CS-100 allows for delineation of mild to moderate CAD from significant CAD and lesion severity post angiography to make a proper decision for percutaneous coronary angioplasty (PCI). Using time tested Framingham risk scoring model as the background we developed a modification scoring system **(Table 1)** to apply to raw MCG score and CS-100 analysis to improve the specificity and sensitivity and applied it prospectively in clinical evaluation of patients presenting in various stages of coronary ischemia.

Table 1. CS-100 modification score calculation table.

Symptomatic female 30-50 years with dysautonomia (MVP, Migraine) and hormone imbalance/no Framingham risk factors	Female: 30-50 years Classic CAD symptoms/+1 Framingham risk factor	>2 Framingham risk factors asymptomatic	Type II diabetes >5 years and uncontrolled DM	Known CAD asymptomatic	Classic CAD Symptoms +2 Framingham risk factors all patients	Significant Stress >2 years with classic CAD symptoms >40 years	Classic CAD Symptoms With no risk factors M>40 years/F>50 years	Atypical symptoms Patients <50 years/no Framingham risk factors
-1	+1	+1	+2	+1	+2	+1	+1	-1

Source: ©Ramesh K. Adiraju, MD, FACC)
MVP: Mitral Valve Prolapse; CAD: Coronary Artery Disease; DM: Diabetes Mellitus
Modification Score: 0-2=Mild risk; 2-4=Moderate risk; 5-9=Significant risk

RENU-CA INSTITUTE CLINICAL EXPERIENCE AND DATA ANALYSIS WITH MCG/CS-100 TESTING

Outpatient screening of patients presenting for CAD was carried out prospectively using MCG/CS100 testing. Patients with known CAD previously treated with PCI, Women and diabetics were included. These are the vulnerable high-risk groups. MCG/CS100 modification was then applied based on Framingham risk factors, DM-II, Women and known CAD as shown in the chart. Treatment plans including coronary angiography were made based on the Modified MCG score or CS-100 analysis. Detailed analysis of the early series of patients tested using MCG between 7/2011 unto 5/2012 are shown in **Chart 1**. MCG scoring scale ranges between 1-10. MCG score of 1-4 is normal, >4 are suggestive of significant CAD.

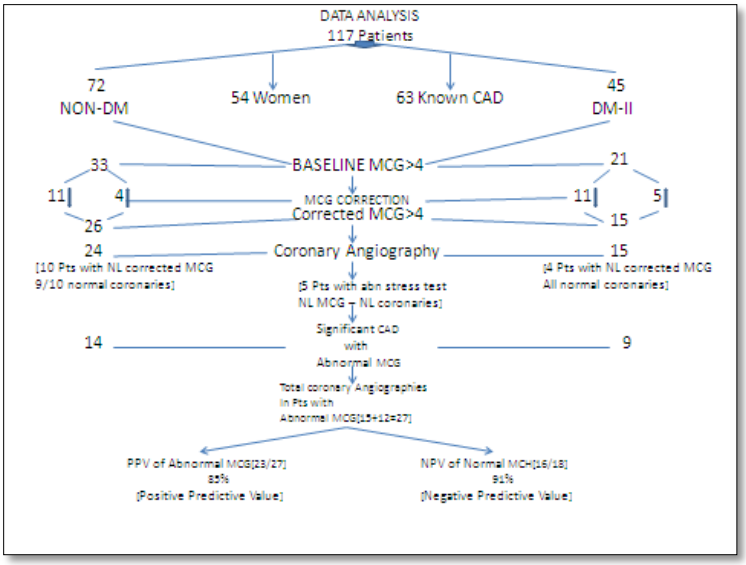


Chart 1. Analysis of the early series of patients tested using MCG between 7/2011 unto 5/2012.

DATA ANALYSIS

Our experience with MCG testing included 353 patients. First 117 patients presenting for CAD evaluation screened with MCG testing were analyzed. 72/117 was non-diabetics, 45/117 had diabetes and 63/117 had known previous CAD that was treated. There were 54 women in the group. The ages ranged between 30-80 years. This is a good spectrum of patient population reflecting real world experience including the so called high risk groups. Only 11/117 was subjected to other non-invasive testing modalities, primarily nuclear perfusions scan imaging. Three patients had stress ECHO evaluation. By current standard of care 99/117, due to risk factors such as diabetes, women and known CAD patients, would have had extensive non-invasive testing including CCTA. This is a 91% reduction in non-invasive testing which is a significant cost saving for Medicare spending.

54/117 patients had an abnormal MCG score of >4.0 at baseline. After applying our modification factor the corrected MCG score was abnormal in only 40 patients. 14/54 was false positive who would have been subjected to further testing without the modification correction. This is a further 25% reduction in patients that would have otherwise undergone further extensive testing and/or coronary angiography even by standard MCG testing with increase in the overall cost of care. It is important to note that we had some patients who scored low on baseline MCG testing that were abnormal after correction and yet others who scored high at baseline that were downgraded after correction proving that modification factor improves specificity and sensitivity. Since MCG was a novel approach we ended up doing angiography in all these patients. The corrected MCG scores correlated very well with angiographic disease in all these patients validating the safety and efficacy of modified MCG score.

Patients with known previous coronary interventions and women below 50 years with atypical symptoms and normal or borderline abnormal MCG scores between 4.0-5.0 were not recommended any further testing and were followed clinically with confidence. This is a further cost saving strategy based on MCG testing. All these patients are doing well to date on continued medical management and there were no cases of missed significant disease. Among patients with no known previous CAD but had abnormal stress test with classic clinical symptoms who underwent coronary angiography, there were quite a few who did not have OCAD. With increasing confidence in the validity of MCG score and CS-100 and applying modification factor correction these patients can be pre-screened and safely limit coronary angiography for only those who demonstrate abnormal CS-100 or modified MCG score thereby achieving further cost saving in coronary care in the future.

5 patients in the MCG series 2-non-diabetics and 3 diabetics who underwent coronary angiography on the bases of abnormal stress tests, but had normal MCG scores, had no significant CAD at angiography. 10 non-diabetic patients and 4 diabetics who had normal corrected MCG scores but presented with classic clinical symptoms and/or abnormal ECG findings were subjected to direct coronary angiography and no obstructive CAD was found. Again, with increasing confidence in CS-100 or MCG scoring, these patients can be safely managed medically without subjecting them to angiography which will be a huge cost containing measure. Two patients in our series with high MCG scores who were subjected to coronary angiography showed no obstructive CAD. These two patients however had cardiomyopathy (CMP) with ejection fractions <40%. Abnormal CS-100 or MCG testing in these patients can be utilized to the advantage of CMP patient management and follow-up.

Among the patients who had abnormal corrected MCG scores there were 15 non-diabetics and 12 diabetics. All these 27 patients underwent coronary angiography.23/27 (14 non-diabetics and 9 diabetics) had significant OCAD at coronary angiography for a positive predictive value of 85%. 18 patients in all in this series were subjected to coronary angiography due to abnormal stress test [11] or unstable clinical presentation or an abnormal baseline MCG score. 16/18 of these patients with normal corrected MSG scores showed no obstructive CAD at angiography for a negative predictive value of 91%.

Out of the 11 patients in our series who underwent nuclear stress testing or stress ECHO 8 underwent coronary angiography. 5/11 of were diabetics and 6/11 were non-diabetics. The outcomes of these 11 patients are charted in **Chart 2**.

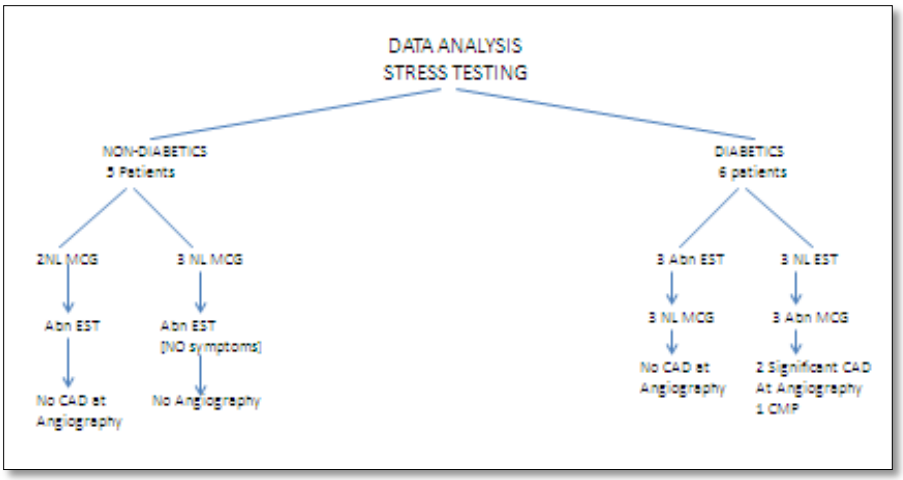


Chart 2. Analysis of 11 patients who underwent nuclear stress testing.

Without corrected MCG scoring 8/11 – 73% would have undergone coronary angiography a poor yield for significant CAD with increased cost of care. 2/11 who had significant CAD was women with known CAD. They were identified accurately by modified MCG scoring but had false negative stress tests. These patients would be at risk for sudden cardiac events without MCG scoring which increases their mortality and morbidity with increased cost of long term care.

These findings from our series, even though small numbers are in line with the findings from recent NCDR data registry analysis published from Duke.

9 patients from our series with known complex CAD s/p recent PCIs who presented with new classic angina symptoms were successfully managed medically, without any further investigations, based on modified MCG scores without any untoward outcomes to date. One of these patients had coronary angiography due to a syncopal episode and was found to have patent previous PCI sites and stable CAD. Medical management was continued.

3 patients who had PCI based on abnormal MCG score in our series had follow-up MCG testing showing normal MCG scores.

One of the patients is a diabetic woman, post bypass surgery with progressive CAD who was managed with multi-vessel PCIs, a complex case, showed an increase in her MCG score after initial normalization of MCG score. During angiography she had no significant change in her anatomy with stent across a bifurcation point in the circumflex coronary artery and some angiographically unimpressive distal stenosis. FFR assessment of this area demonstrated a drop in FFR from 1.03 to 0.82 distal to the stent. This is a borderline indication for PCI as per FAME trial recommendations. Due to a recent increase in MCG score we intervened on the distal LCx lesion that relieved her anginal symptoms. This is an example of a complex coronary scenario where MCG score was used as an adjunct to FFR to help make the right decision. This is also a case in point where ACC/AUC guidelines cannot be adhered to without risking a fatal coronary event. If not intervened on the distal stenosis this patient would have progressed to In-stent restenosis with thrombosis of the proximal stent that could have been a life-threatening event. MCG testing in her case helped us proceed in the right direction. Three other patients with known significant CAD history who had classic symptoms, but negative stress tests had baseline MCG score in the normal range but abnormal modified MCG. All three of these patients had significant progression of CAD at angiography requiring coronary intervention. One of them required coronary bypass grafting. Among the 11 patients who underwent stress testing 8 had abnormal stress tests. 3/8 of these patients did not undergo coronary angiography due to lack clinical symptoms. 5/8 underwent coronary angiography and showed no significant CAD. Three patients who had normal stress tests, but abnormal MCG score were subjected to coronary angiography and had significant CAD. Abnormal MCG score delineated significant CAD irrespective of the stress test results in all 8 patients.

63/117 patients screened were patients with known CAD, 45 diabetics and 54 women. All these sub-groups are considered high risk groups. These patients in the normal course would have undergone a series of investigations and 65-70% of them despite the testing would have had coronary angiography and unnecessary PCIs. Some of these patients with significant disease particularly women and diabetics due to false negative test results, as shown in our series may not undergo angiography which can be risky. The incidence of sudden cardiac death is higher in women and diabetics and 50% of women manifest sudden death as the first presentation of their CAD. Our series included a fair share of women and diabetics and yet showed a high positive and negative predictive value across the board. Modified CS-100 or MCG scoring is more sensitive than perfusion imaging in

identifying significant CAD particularly in women.

47 non-diabetics and 21 diabetics, 33 of whom were women, who had known previous CAD, were evaluated by just MCG testing and managed medically. These patients were safely followed clinically and managed medically due to normal modified MCG scores and atypical clinical symptoms. CAD is the leading cause for mortality and morbidity, and is a major offender of health care spending alongside type II diabetes. Women and diabetics are high risk sub-groups that present with fatal clinical manifestation of CAD without warning and are not well delineated by current modalities of testing as observed in published data. We observed Modified CS-100/MCG scoring to be particularly useful in Women and diabetics. Cardiovascular disease behaves differently in Women and most previously published cardiovascular literature has had poor representation of Women. MCG scoring, we believe is therefore particularly sensitive and specific as a general screening test as well as a reliable test for decision making in the management of CAD in Women and diabetics.

Even though our series with CS-100 and MCG testing is a single center, non-randomized experience and the sample size is relatively small the findings mirror the observations from recent published data such as Duke NCDR registry analysis. Most studies in the literature on coronary ischemia and ischemic cardiomyopathy evaluations including the earlier studies on MCG testing have been on patients scheduled to under coronary angiography. This can potentially create a selection bias. Our series is a real-world experience including all comers and high-risk groups. The main goal of our endeavor was to find a reliable, optimal and safe way to avoid unnecessary, expensive and redundant investigations and therapeutic modalities in the management of Coronary Artery Disease.

After early experience with MCG testing we evaluated CS-100 system for CAD screening and known CAD patient management from 2014 to 2017. CS-100 is based on the same mathematical principles as MCG and uses the same database as MCG but has the additional capability of delineating specific coronary artery distribution and the severity of stenosis due to comprehensive 12 lead analyses that represents complete coronary anatomic territories. In our extensive experience with CS-100 in over 700 cases we were able to localize coronary ischemia specific to even branch vessel disease in many patients using CS-100 localization with angiographic correlation. It is also a system that has the master grid data built into the computer at the site of testing and generates final analysis instantly for reading like perfusion imaging with pictorial display of the coronary artery distribution and myocardium in jeopardy as opposed to MCG score that is generated remotely after online transmission of raw data from patient to a central location. CS-100 is therefore next generation MCG and is more advanced and comprehensive. CS-100 is also a practical alternative to invasive FFR and IVUS as it can be performed during coronary angiography with instant reading for significant ischemia assessment in a specific coronary artery stenosis. CS-100 is therefore a non-invasive modality comparable to FFRct in its ability to localize specific coronary stenosis and its severity. We also encountered less false negatives and false positives with CS-100 testing compared to MCG due to more detailed additional 12 lead analysis.

At RENU-CA Research Institute, we have identified dysautonomia as a crux abnormality underlying type ll diabetes, metabolic syndrome, sleep apnea syndrome, labile uncontrolled hypertension and atherosclerosis [33,34]. Vascular inflammation and endothelial dysfunction have been identified as the underlying pathophysiologic derangements in atherosclerosis and CAD. Major clinical trials are in progress currently for evaluating this hypothesis. However, the major emphasis in these investigations has been treating the inflammation to reduce CAD and atherosclerosis progression. Vascular inflammation and abnormal vasoreactivity we believe are triggered by dysautonomia induced vascular endothelial cell dysfunction and cyclic guanosine monophosphate (cGMP) nitric oxide pathway inhibition [40,41]. Dysautonomia treatment algorithms have been implemented successfully at RENU-CA institute over the last 13 years in management of these conditions with good clinical outcomes [33,34]. In keeping with our goals of cost affective optimal care at RENU-CA institute, we adapted a novel non-invasive coronary ischemia screening and CAD evaluation protocol using the CS-100 Frequency Cardiograph (FCG) analysis system.

FCG-CS-100 analysis is a unique non-invasive modality, as discussed above, for assessment of coronary blood flow and myocardial function. Like FFR, CS-100 is based on sound mathematical principles and their reference database is extensively validated in over 27,000 patients. CS-100-FCG is comparable to FFR in assessing functional significance of CAD as it is based on mathematical analysis of dynamic data that provide specific information on coronary blood flow and myocardial function simultaneously, 12 lead analyses allows localization of specific coronary artery involved like CT angiography. Even though CS-100 has been predominantly used in CAD assessment due to its ability to identify myocardial function, we have utilized CS-100 patterns in identifying patients with cardiomyopathy and diffuse vascular inflammation for treatment decisions and follow-up prognostication of treatment programs implemented in these patients. CS-100 is a simple, patient-friendly non-invasive testing modality that is relatively easy to conduct and inexpensive to administer. CS-100 is a very sensitive and specific tool in assessing the functional significance of OCAD in resting state thereby allowing appropriate delineation of mild to moderate CAD from significant CAD. Hence, CS-100 is very effective, safe and inexpensive, modality for CAD assessment. CS-100 can be

safely used in decision making for coronary angiography and subsequent PCI after angiography in patients presenting with acute coronary syndrome thereby avoiding unnecessary coronary angiography and PCIs. CS-100 system is a very simple and portable laptop based system with capability of instant analysis and results. Therefore, CS-100 is portable and is both physician and patient friendly. Minimal technical skills are required to perform the study. CS-100 is an office based testing modality but can also be performed in the emergency room setting, or during coronary angiography simultaneously for assessment of functional significance of a coronary stenosis. This can be a viable alternate to FFR/IVUS during coronary angiography and avoids invasive risk and operator bias in committing to unnecessary PCI. CS-100 is much less cumbersome, more easily portable and simple testing modality compared to noninvasive FFRct. FFRct has recently been approved by CMS for non-invasive CAD assessment. FFRct involves CT scanning that can be intimidating to the patient and is not freely accessible to all. CS-100 is more cost effective and patient friendly.

Applications of CS-100 include

1) Screening for CAD in the general population in a physician's office or emergency room setting.
2) Identifying active/significant CAD progression or active of coronary ischemia in patients with known CAD with symptoms of angina and ischemia prior to committing to coronary angiography.
3) Segregating patients with mild/moderate/significant CAD to expedite prompt management strategies while avoiding unnecessary expensive investigations and invasive treatment approaches. This is achieved without the risk of missing significant CAD due to high specificity and sensitivity. This approach is particularly appropriate for the current times when cost containment in medicine is imperative and the available modalities of testing such as CCTA, Nuclear stress testing and cardiac MRI are expensive with a suboptimal clinical yield.
4) Aiding in decision making for coronary angiography and appropriate PCI. CS100 can be an adjunct or alternate to FFR/IVUS strategy. It is obviously less expensive, non-invasive and can be more easily implemented widely than FFR/IVUS.
5) Assessing acute coronary syndromes, in proper triage and avoiding unnecessary hospitalizations and expensive testing and unnecessary commitment to angiography.

Framingham risk factors and risk scoring have stood the test of time and are very reliable. They are more effective than non-invasive testing in improving the positive predictive value for significant CAD at angiography as demonstrated in the recent NCDR registry data analysis by Patel et al. [2]. Framingham risk criteria based scoring for 10 year coronary heart disease (CHD) risk has been developed for women and adults. These scores have been applied to categorize patients into low-, intermediate- and high-risk groups. However, because CAD is the leading cause of mortality, and the unpredictability of CAD particularly in high risk groups such as women, diabetics and patients with >2 Framingham risks, coronary angiography has become the gold standard and a safe final common pathway in CAD management. This has increased the cost of care for high-risk groups and cardiac patients exponentially without commensurate clinical benefit. Abnormal vascular reactivity increases the risk for sudden cardiac events and renders non-invasive coronary ischemia evaluation modalities and FFR unreliable particularly in high-risk groups such as diabetics and women with diffuse CAD.

METHODS

At RENU-CA Research Institute, we adopted CS-100 testing for CAD management due to growing concerns about efficacy of current modalities of testing and inappropriate use of coronary angiography and PCI. The CS-100-FCG system utilizes cardio-electrical data generated from 12-leads and 2-leads electrodes. A portable device at the point of care records multiple cycles of complete resting ECG analog signals from 12 leads over 80-90 s duration. Digitization, encryption, Fast Fourier Transformation of the raw data and mathematical transformations of the data and their comparison to database is all built into the system unit at the point of care. The data is then compiled and a total of 113 indexes (60 indexes @5/lead from 12 leads and 53 indexes from 2 leads) are compared against 27,000 empirical databases that are built-in into the system. CS-100 is therefore a comprehensive and compact system and is widely applicable. It can also isolate individual coronary artery territory at risk like angiography due to standard 12 lead analyses.

Low yield and false positive coronary nuclear perfusion imaging in women and diabetics both of whom are vulnerable groups for silent untoward coronary events as demonstrated in DUKE study of NCDR registry is common. We believe the reason for false positivity in Diabetics and Women during provocative testing modalities such as stress perfusion is due to vascular inflammation and abnormal vasoreactivity from endothelial dysfunction. This is based on our research work with Dysautonomia in Type II diabetes and vasculopathy [29,30]. Diffuse pattern abnormality with CS-100 testing in these patients was associated with diffuse coronary vasculitis and non-critical disease. This is a pattern that can potentially be evaluated as a marker for vascular inflammation and non-ischemic myocardial dysfunction in the future. Using time tested Framingham risk scoring model as the background, we developed a modification scoring system to improve the specificity and sensitivity and applied it prospectively in clinical evaluation of patients presenting in various stages of coronary ischemia with CS-100 analysis.

The CS-100 testing analyses consists of 4 index leads (Lead I, AVR and V1, V2) that assess presence of CAD, good for screening. There are also 12 lead analyses that correlate with standard EKG analysis to delineate specific coronary artery territory involved and the severity of involvement. This allows CS-100 the capability to delineate specific coronary artery territory involved and can give lesion specific severity information in the assessment of known CAD patients post coronary angiography. The CS-100 as noted above has a database built into the system at site hence analysis and final diagnosis are generated immediately as the test is performed for instant results. Hence CS-100 can be utilized as a tool to assess significance of coronary artery stenosis real time during coronary angiography like FFR and CTA-FFR. CS-100 is very portable and non-invasive therefore has advantage over invasive FFR and CTA-FFR.

RESULTS

Office based screening of patients presenting for CAD was carried out prospectively using CS-100 testing. Patients with known CAD previously treated with PCI, Women and diabetics were included. These are the vulnerable high-risk groups. CS100 modification was then applied based on Framingham risk factors, DM-II, female gender and known CAD as shown in the **Table 1**. Treatment plans including coronary angiography were made based on the Modified score. There were no exclusion criteria, all patients presenting to the clinic with signs and symptoms of coronary artery disease and patients with known coronary artery disease with and without active symptoms were interviewed and informed verbal consent obtained for CS-100 testing after explanation of the CS-100 testing modality. CS-100 testing results were then explained and discussed with the patients. Even patients with active significant symptoms were included as CS-100 testing is a simple, patient friendly and easy to perform test with no provocation of coronary ischemia as is done with other non-invasive testing modalities such as SPECT (single photon emission computerized tomography) nuclear perfusion imaging). Even in patients presenting with unstable symptoms quick CS-100 screening was carried out prior to hospitalization. This availed us with the possibility of comparing coronary angiography findings to the prior CS-100 results prospectively. In our initial experience with the first 100 patients with known CAD and ones with classic angina symptoms SPECT perfusion imaging was also carried out simultaneously for comparison and angiography was pursued when the suspicion was high for active CAD. With good correlation to angiography and gaining confidence in the reliability of CS-100 findings we relied on CS-100 testing to delineate mild to moderate CAD from significant CAD. This approach allowed us to avoid unnecessary hospitalizations and coronary angiography in patients evaluated for CAD with confidence. We also used CS-100 testing to determine functional significance of known coronary stenosis, in patients who have had prior coronary angiography who were symptomatic, too successfully and safely avoid unnecessary coronary interventions. CS-100 testing in symptomatic patients presenting with active angina, but low index of probability for CAD by accepted clinical parameters such as young age <40 years and unremarkable EKG, was accurate in identifying significant CAD confirmed by coronary angiography in our experience. These patients underwent coronary revascularizations and had follow-up CS-100 studies that demonstrated resolution of the initial abnormality (case examples TB(f), SN(m), RB(f)). Over 700 patients have been studied with CS-100 testing from January 2014 to August 2017 at RENU-CA research Institute. They include the whole spectrum of CAD manifestations including ACS (Acute coronary syndromes). We have been able to avoid expensive, elaborate non-invasive testing modalities such as nuclear stress testing, cardiac CTA and coronary calcium scoring successfully in our practice and have been able to cut down unnecessary coronary angiographies and angioplasties confidently and safely.

Future large scale multi center trials using CS-100 testing protocol are required particularly in high risk groups such as diabetics, women and complex CAD patients where currently available modalities have proven to ineffective as demonstrated in recently published data. Some of the proposals for future studies with CS-100 testing are as follows:

1) Outpatient screening and treatment strategies for CAD.
2) CS-100 based triage for ACS and USA patients in the Emergency Wards.
3) Delineating mild to moderate CAD from significant CAD. This is an important distinction as recent literature demonstrated safety of optimal medical management in the mild to moderate group while significant CAD carries a high mortality and morbidity burden if not intervened expeditiously.
4) Hibernating myocardium assessment and ischemic cardiomyopathy management strategy to improve left ventricular systolic function.
5) CS-100 scoring for identification and effective management of CAD in high risk Women and diabetics.
6) CS-100 can also be used very effectively, as we demonstrated in our experience, as a non-invasive alternate to invasive Fractional Flow Reserve (FFR) for assessment of functional significance obstructive coronary artery disease diagnosed by CCTA or invasive angiography prior to PCI and avoid unnecessary coronary interventions.

DISCUSSION

We believe CS-100 is a cost effective and simple yet sensitive modality that can be an alternate to Computed

Tomography derived fractional flow reserve (FFRct), FFRCT or cFFR technology that is being developed as an alternate to invasive FFR by angiography for assessment of functional significance of obstructive CAD demonstrated by angiography or CCTA. CS-100 has added advantages for being very simple to use, less cumbersome and portable to office based or emergency room setting. In our experience, we have demonstrated CS-100 to be very sensitive and specific in evaluation of CAD across the spectrum of CAD presentations including high risk groups such as type II diabetics and Women and known CAD patients. CS-100 has also proved to be a reliable modality in differentiating mild to moderate CAD from significant CAD. This differentiation has both clinical and cost-effective implications in long-term management of coronary artery disease patients. We therefore feel confident in recommending CS-100 testing for CAD screening in all scenarios. CS-100 is a mathematically based assessment like FFR and evaluates myocardial function and compliance. It can also be an effective tool for assessing hibernating myocardium in ischemic cardiomyopathy and revascularization strategy during PCI as an adjunct or alternate to FFR. These are arguably very challenging areas in cardiology were decision making is crucial due to critical outcomes and high mortality at stake. Currently prohibitively expensive modalities of assessment such as PET scanning and cardiac MRI in ischemic cardiomyopathy and FFR/IVUS during PCI are being utilized. These modalities are effective but are expensive and have limitations for wide applicability in the community. We also developed a more specific scoring protocol for CS-100 as demonstrated below with case examples. Over 700 cases have been tested since 2014 at RENU-CA Research Institute. They include the whole spectrum of CAD manifestations including ACS (acute coronary syndromes). We have been able to avoid expensive, elaborate non-invasive testing modalities such as nuclear stress testing, cardiac CTA and coronary calcium scoring successfully in our practice and have been able to cut down unnecessary coronary angiographies and angioplasties confidently and safely. False negative result missing significant CAD jeopardizing patient safety has been zero in our series to date. On the contrary, we have several case examples of patients with significant CAD, who were missed during emergency room evaluations or by nuclear stress testing, by using CS-100 evaluation we could make accurate diagnosis with appropriate care delivery. We also have successfully used CS-100 evaluation to follow patients with known CAD and patients with significant CAD risk factors and avoid unnecessary hospitalizations and coronary angiography safely and effectively.

We have identified false positivity with CS100 testing in certain sub-group of patients. These sub-groups in our series were Women, T2DM patients and patients with systemic inflammatory conditions. Interestingly most of these patients had dysautonomia; this could be an element of selection bias as RENU-CA research Institute is a dysautonomia research center also. However, this I believe is an intriguing finding in the era of systemic vascular inflammation being identified as a significant contributor to vascular atherosclerosis. Based on our comfort with management of dysautonomia we have treated these sub-groups of patients with autonomic regulation and optimal medical therapy and demonstrated improved CS100 abnormality thereby avoiding high cost extensive investigations and invasive cardiac procedures that are currently implemented in these high-risk groups. Case examples of patients with significant false positive test are also included.

Future large scale multi-center randomization of high risk groups to current standard of care vs. CS100 and autonomic dysfunction assessment based protocol management strategy is warranted. Applying the modification score to stratify patients into mild moderate and significant CAD categories is useful in implementation of care based on CS100 analysis in patients presenting with wide range of CAD spectrum. We are optimistic, with the recent CMS recognition of HeartFlow FFRct system for reimbursement based on its non-invasive approach and cost saving in CAD management, that CS-100 which is less cumbersome, simple for patient and physician to use, non-intimidating and more portable that can be used during coronary angiography, will be viewed as less cost of care and more widely applicable for acute care and long-term management of coronary artery disease patients. Combining with dysautonomia assessment and treatment protocols CS-100 can be a modality for comprehensive and cost-effective care for Type II diabetes and cardiovascular diseases management.

Chart II – CS100 scoring protocol (Source: ©Ramesh K Adiraju, MD, FACC)

I. Abnormal range segments 1-16 for 12 lead indexes
   - Mild=4
   - Moderate=8
   - Significant=8-12
   - Possible Scar=>14 or false positive.

II. 2 lead indexes score: Marker for presence of CAD
   - 1, aVR=1+1=2
   - V1, V2=1+1=2

1-2 remote CAD, 2-4 active CAD.

Composite score per lead:

- Mild to Moderate=4-8 (Medical Management)
- <4=Non-specific, Normal
- >8=Significant Ischemia
- >14=Possible Scar or false positive.

III. Coronary artery localization

- RCA (right coronary artery)=II, III, aVF, V5-6
- LCX (left circumflex)/Diagonal=V4-6, I, aVL
- LAD (left anterior descending)=
  i. Proximal=V2-5, I
  ii. General LAD=V2-6, I, aVL
- Multi-vessel Territory=>7 leads

Scoring protocol (Source: ©Ramesh K Adiraju, MD, FACC)

Step I: Number of boxes involved in the abnormal range for each of the 12 lead Power spectral domains is tabulated.

Step II: Add abnormal 2 lead index scores.

Step III: Coronary localization based on >3 lead scores per coronary territory.

The CS100 score obtained from the testing is then correlated with the Modification score calculated according to the CS-100 modification score table to determine active CAD, mild to moderate vs. significant CAD and the ischemic burden to aid optimal clinical decision process.

CASE EXAMPLES

1. Patient Name: SD

Step I: V5=12

V6=16

Step II: 2 Leads Score=1 Borderline

Step III: Coronary Localization=2 Leads only, Borderline LCX

CS100 modification: (Female, Obese, >50 years, Asymptomatic, >2 Framingham Risks, No CAD History) Modified Score=1.

Therefore, Non-critical – Medical Management.

2. Patient Name: SM

Step I: 3 Abnormal Leads

aVL=3

III=3

V6=16

Step II: 2 Lead Index Score=0

Step III: 3 Leads – Borderline.

V6=16, Possible Scar

CS100 modification: (Male, >60 years, Asymptomatic, >2 Framingham Risks, Known CAD History) Modified Score=3.

Borderline. Medical Management.

3. Patient Name: EM

Step I: 5 Abnormal Leads

II=16

III=2

aVL=4

V5=9

V6=5

Step II: 2 Lead Index Score=2 Significant.

Step III: II, III, aVL V5-6, RCA Significant Disease, LCX.

CS100 modification: (Male, >60 years, Symptomatic, >2 Framingham Risks, Known CAD history) Modified Score=7.

Significant. Angiography positive, significant disease/PCI.

4. Patient Name: SH

Step I: 2 Abnormal Leads

I=1

aVL=16

Step II: 2 Lead Index Score=1 Borderline

Step III: Coronary Localization I, aVL=LCX

CS100 modification: (Female, >50 years, Symptomatic, >2 Framingham Risks, no CAD history, Metabolic Syndrome) Modified Score=7 Significant.

Angiography positive, significant disease/PCI.

5. Patient Name: TB

Step I: 3 Abnormal Leads – V4, 5, 6 – 3, 4, 5 blocks.

Step II: Lead Index Score=1 Borderline.

Step III: Coronary Localization=Lateral branch.

CS100 modification: (Female, 68 years, Asymptomatic, Framingham risk score 0, no CAD history.

Coronary angiography shows small diagonal branch disease.

6. Patient Name: LH

Step I: 1 Abnormal Lead lll – 2 blks.

Step II: Lead Index Score=0.

Step III: None.

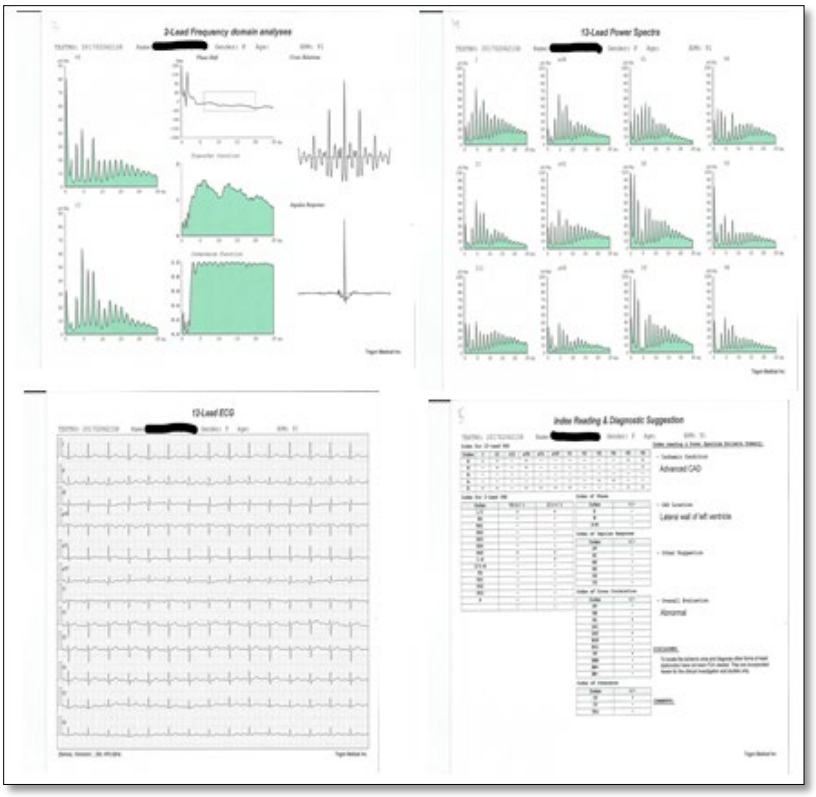
CS100 modification: 64 years old Female, Strong family history, 2Framingham risks, known coronary branch vessel disease with mild symptoms.

CS100 score is normal=Medical management no coronary angiogram.

CLINICAL EXAMPLES CS100 STUDIES

Normal Study Pattern: 12 lead score=0, 2 lead indexes=0

Abnormal Study Pattern: 12 lead score=>12 in 7 leads. 2 lead index=3



Clinical case study

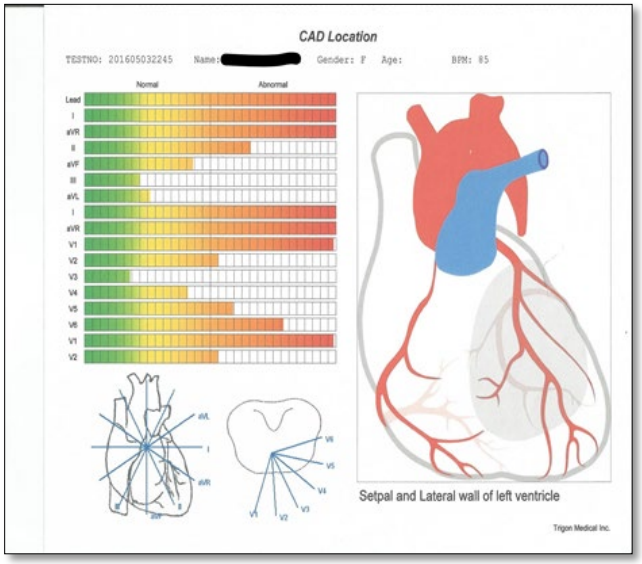
DT- 54 years old female, War veteran, lost husband severe stress, depression for 2 years (stress induced systemic inflammation and vasculopathy, more common in female patients due to dysautonomia and endothelial dysfunction).

Classic angina 3 weeks- ER visit normal EKG discharged.

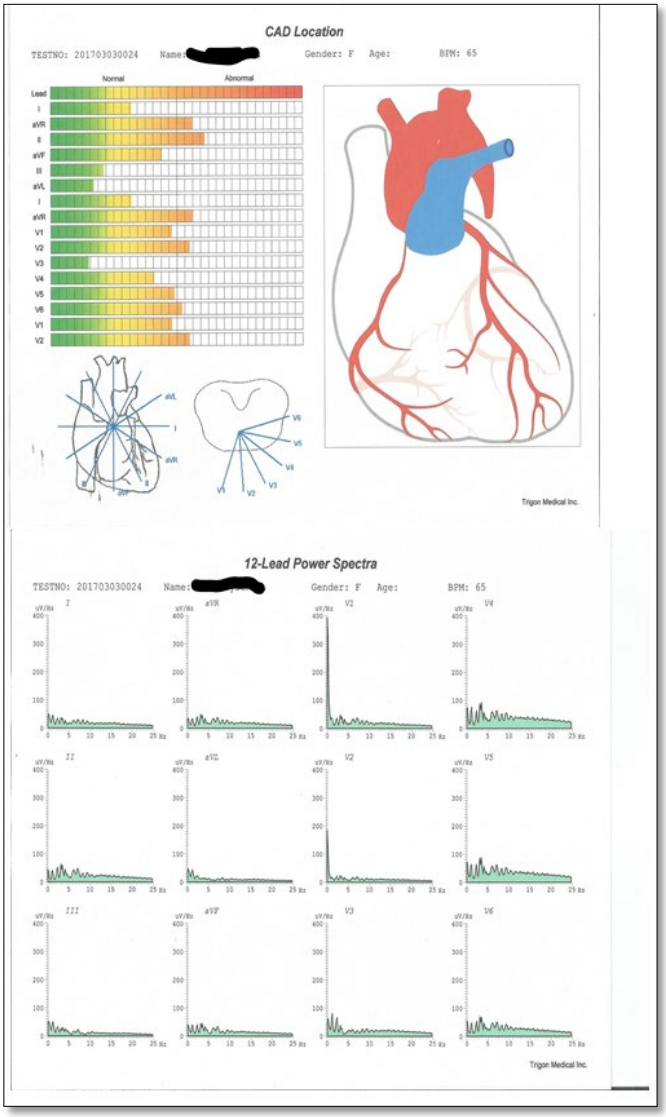
CS-100 abnormal proceeded with coronary angiography.

Coronary Angiography- Critical LAD (left anterior descending) and RCA (right coronary artery) disease. Successful angioplasty/stenting of both LAD and RCA.

CS100 05/2016: Pre-coronary angiography



CS100 03/2017: Post revascularization



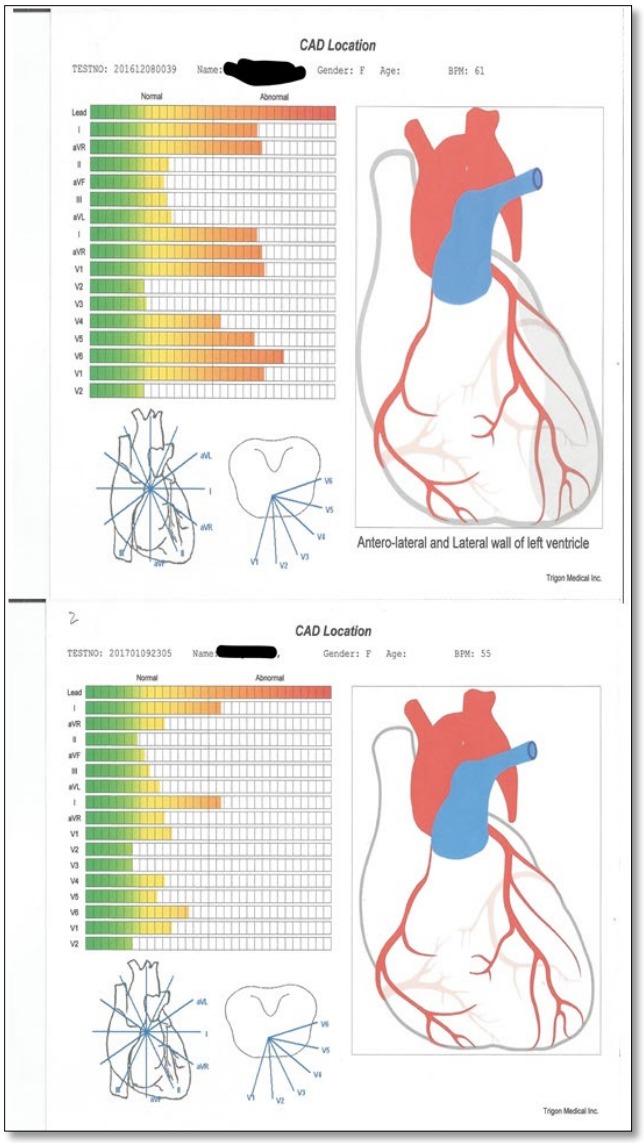
Clinical case study 2

TB- 39 years old female, smoker, chronic severe sinusitis, crescendo angina for 3 weeks, high hsCRP>15, 3 Emergency room evaluations normal EKGs discharged due to low index of suspicion for CAD by standard assessment. Stress testing during one of the hospital visits negative for ischemia.

Presented to office with persistent symptoms.

CS100 pre-coronary angiography: 12/2016. Coronary angiography: Critical LAD (left anterior descending) Diagonal bifurcation stenosis. Successfully treated with bifurcation stenting.

CS-100 post coronary intervention dated 01/2017 showing normal study.

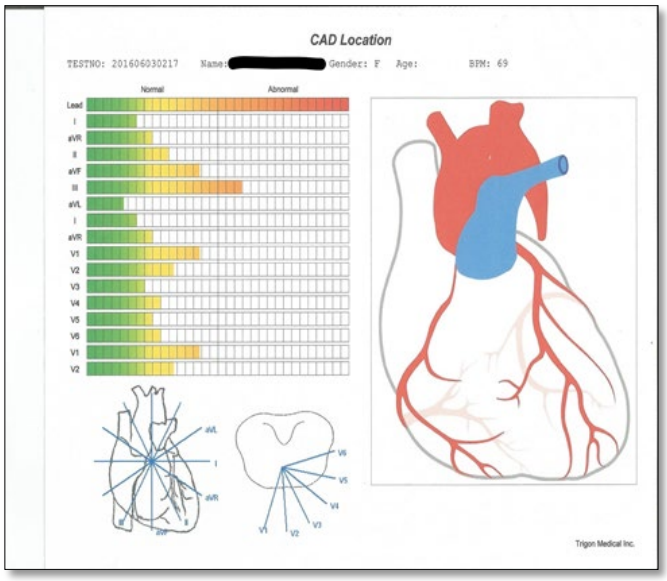


Clinical case study 3

AK- 45 years old female post-Acute myocardial infarction cardiogenic shock, Multi-vessel CAD. Successful multi-vessel coronary angioplasty with Impella hemodynamic support.

Follow-up CS100 after 3 months for mild dyspnea and chest pain evaluation: CS100 score=1 lead, lead lll - 3 blocks. Index lead score=0. Mild. No further testing.

Clinical follow-up 1 year 6 months 09/2017 normal LV function asymptomatic and stable.



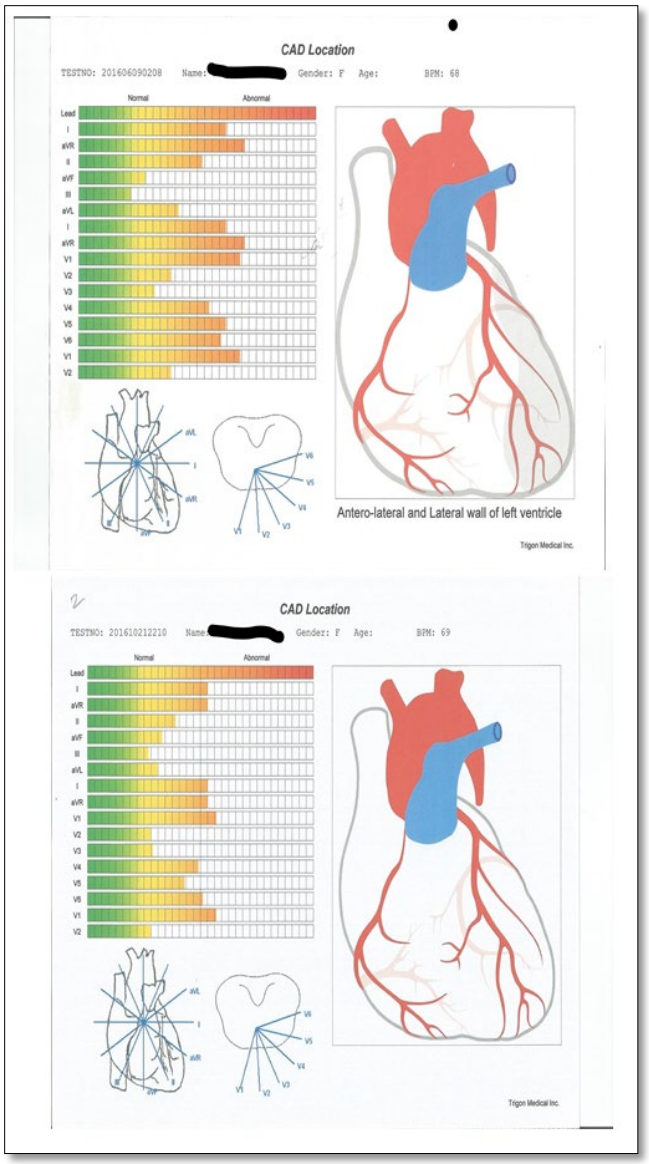
Case study 4

DB- 68 years old female, hypertension, T2DM, hypertriglyceridemia. Significant emotional stress from husband with recent stroke, paralyzed, stress induced dysautonomia and vasculopathy. Classic angina nocturnal dyspnea for 3 weeks.

CS100: 06/2016 – 12 leads score 9 leads <6 blocks, moderate CAD. 2 lead index=2 borderline active disease. CS100 Modification score=5 borderline significant.

Patient diagnosed with dysautonomia and placed on optimal medical therapy with vascular inflammation protocol. Follow-up CS100 4 months later- 10/2016 – Significant improvement in score. Mild CAD.

No coronary angiography or further testing.



Case study 5

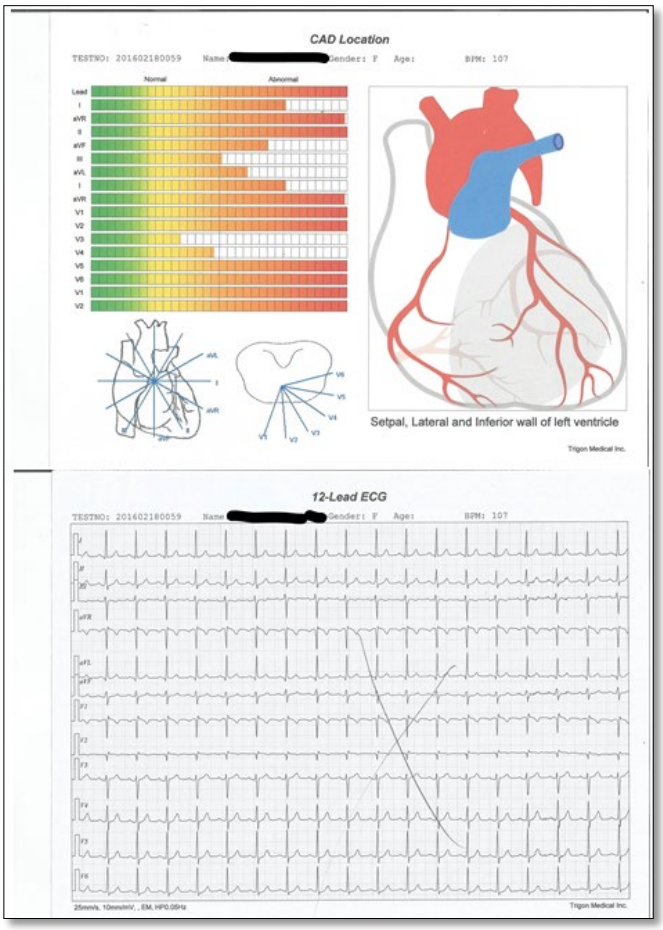
SB- 56 years old Female severe dysautonomia with orthostatic hypotension and labile accelerated hypertension. Pulmonary sarcoidosis. History of Immune antibodies post plasmapheresis. Severe systemic inflammatory process.

Classic angina and shortness of breath × 3 months. Hospitalization for acute congestive heart failure.

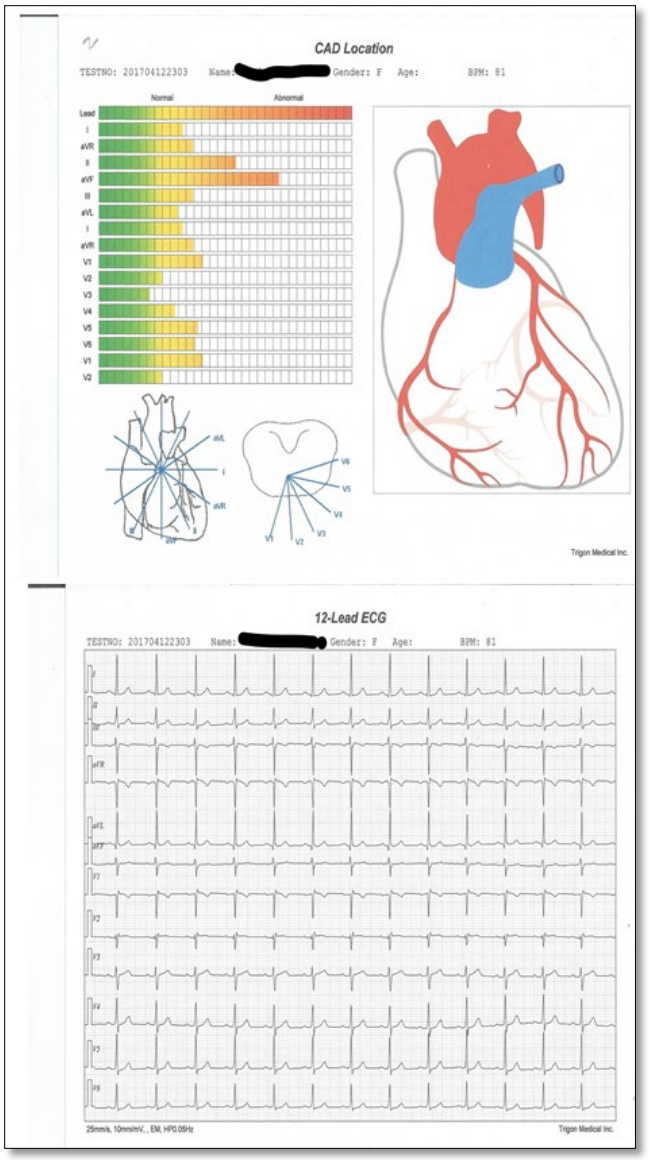
2D ECHO of the heart with dilated Left Ventricle with Ejection Fraction <30%.

CS100 – 02/2016: Marked abnormality. 12 lead scores 16 in >9 leads.

EKG – Normal. Discordance.



Repeat CS100 04/2017 – After medical treatment for dysautonomia and vascular inflammation protocol.



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