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HOME-BASED VIDEOPETHYSMOGRAPHIC DETECTION OF ATRIAL FIBRILLATION

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1. PURPOSE OF THE STUDY AND BACKGROUND

The clinical, economic and scientific challenges associated with AF triggered the National Heart, Lung and Blood Institute to convene a panel of experts to recommend research directions and strategies for AF prevention.[1] The panel defined recommendations in six well-defined fields of research including "the improvement of AF detection by using emerging methods and technologies".

1.1 Purpose of the study

We propose to evaluate the robustness of a novel technology used at home for AF detection that is innovative because it is less intrusive than current monitoring options (contactless) and inexpensive. We believe this novel monitoring strategy could address the current challenge of modern medicine around the detection of sub-clinical AF.

1.2 Background

We propose to shift the paradigm of clinical management of AF patients by using a unique and novel monitoring technology that will be easily and readily available to patients (by downloading an application on a smart device embedding a web camera, without the need for additional sensors), and therefore will enable ubiquitous and contactless testing of individuals with risk to develop AF. We believe the proposed technology could be used for the detection of sub-clinical AF. Approximately 15% of ischemic strokes are directly attributed to emboli in the setting of AF. And, nearly 25% of additional ischemic strokes in which no cause can be identified may also be due to asymptomatic AF.[2,3] Healey et al[4] described the incidence of sub-clinical AF in a large cohort of patients who had undergone recent implantation of a pacemaker or defibrillator; these patients were at high risk for stroke and did not have a known history of AF. By 3-month follow-up, 10.1% of patients had an AF event documented by the device, and AF occurrence was associated with a significant increased risk of ischemic stroke or systemic embolism. Therefore, a substantial percentage of patients with AF have no symptom even during sustained episodes of AF. These characteristics of AF make its detection a real challenge that is not addressed by the current monitoring solutions.

This ineffectiveness of current monitoring strategies for the detection of sub-clinical AF has also been highlighted in the CRYSTAL AF clinical trial.[5] In this study, the patients with a history of cryptogenic stroke but with no clinical history of AF were randomized to conventional follow-up versus implantable cardiac monitor. AF was detected in 8.9% and 1.4% of patients with implantable cardiac monitor and conventional follow-up, respectively. This study demonstrates the importance of developing methods that allow for more ubiquitous monitoring. Recent data have suggested that even short episodes of sub-clinical AF can have devastating clinical consequences. Patients with newly implanted pacemakers with detected AF episodes ≥ 5 minutes had a significant increase in cardiovascular mortality and stroke mortality. This data again emphasizes the importance of detecting all sub-clinical episodes of AF even if the episodes are of very short duration.[11]

1.3 Objectives

Our primary aim is to assess the performance of the Videopethysmographic (VPG) technique of the face and finger to detect AF using a tablet operated by the patient at home. Simultaneous ECG recordings using a continuous recorder that is an ECG patch device will validate the presence of AF at the time of the video recording.

Our secondary aim is to investigate the benefit of acquiring a VPG recording just after successful AF cardioversion/ablation in sinus rhythm. We will evaluate if the VPG-based signal measured during sinus rhythm can be used to improve (in comparison to the results of AIM 1) the detection of early-recurrence of AF events.

Our tertiary aim is to estimate the distribution of the time from first onset of AF (as detected via ECG) until the first true AF detection by VPG. Of particular interest is the probability of detecting AF within 48 hours after the onset of the arrhythmia, which can be viewed as a 48-hour sensitivity of the VPG monitoring process. Similarly,

we will estimate the distribution of the time from hospital discharge (in sinus rhythm) until the first false AF detection by VPG. Each point on the latter curve can be interpreted as the specificity of the VPG monitoring process as a function of follow-up time.

1.4 Study Device/Supplies Administration

The Project Manager will be responsible for receipt, storage, dispensing, collection, accountability and disposal of all program devices and supplies. All devices and supplies will be identified by their specific Model, Serial, and/or Part Numbers; and will be tracked using an equipment/supplies inventory computer program resident in the ECG Core Laboratory (ECL) of the Heart Research Follow-up Program. All equipment and supplies will be logged in the system, and monitored by the Project Manager. The ECL IT manager will be responsible for maintaining all equipment required for the conduct of the study. All devices and supplies will be stored in the ECL secure storage room.

2. STUDY DESIGN

2.1 Overview

In this proposal, we plan to evaluate the technology when used by patients at home. One of the major challenges in designing the proposed study is to ensure that one can capture ECG and video recordings during AF in ambulatory patients while minimizing the size of the patient cohort and the duration of the follow-up period.

2.2 Rational for study design

We will provide a Samsung Tablet (Tab III) or an iPad to the enrolled subjects before they are released from the hospital. Mobile smart devices are used ~3 hours per day on average, and we will use this time spent on the device to capture VPG signals. Indeed, our technology, when installed on a tablet, can run in the background. The application will automatically be triggered when the subject switches on the device, and while the subject interacts with the device during internet browsing or watching videos . This recording concept will provide previously unattainable streams of data, with no limit in recording duration and number of recording sessions, to analyze pulse variability and identify the presence of AF.

3. CHARACTERISTICS OF THE RESEARCH POPULATION

3.1 Subject Characteristics

We opted to enroll two sets of symptomatic patients with paroxysmal or persistent AF 1) scheduled for ablation treatment), and 2) treated by electrical cardioversion. We selected these cohorts of patients because ~40% of patients with successful AF ablation and ~30% in patients successfully converted by electrical shocks are expected to experience early recurrence of symptomatic AF (ERAF) during the following 14 days. As a note, increasing the follow-up period to 60 days would increase the number of ERAF by only 10%. Oral et al. [8] studied the symptomatic ERAF in 110 patients after ablation treatment (pulmonary vein isolation) for either paroxysmal or persistent AF. Their observational study reported that 35% of the patients had a recurrence of symptomatic ERAF at a mean 3.7+/-3.5 days after the procedure. Figure 4 provides the distribution of the ERAF for a 60-day follow up period. In an independent study, Lee et al. reported 39% of symptomatic ERAF in a cohort of 207 patients who received ablation (focal or isolation procedure) for paroxysmal AF.[9] Recently, Chang et al. characterized symptomatic ERAF in the same type of patient cohort i.e. 339 patients with symptomatic drug-refractory AF treated by ablation. Their work described a 34% of early recurrence of AF in patients with non-paroxysmal AF, and 15% in patients with paroxysmal AF.[10] As reported by Andrade et al. (see Table I in [11]) on the incidence of symptomatic ERAF after ablation, it is not uncommon that patients treated by catheter ablation experience symptomatic ERAF with an incidence between 30% and 50%. For the rate of ERAF in patients with electrical transthoracic cardioversion, the literature is rather poor. Bainconi et al., Yu et al., and Siaplaouras et al. reported ERAF reaching 26%.[12-14]

3.1.1 **Number of subjects:**

The project is designed to gather two sets of data during a period of 35 months: learning and validation. We will acquire the data from the learning group during the first 17 and a half months of the study. During an additional period of the same length, we will enroll the patients for the validation dataset (50% split). We have planned to enroll 315 patients on a 3-year period for the learning and validation groups.

We believe we will not be able to enroll all AF patients coming to the URMC clinic. Based on previous studies (preliminary results) conducted at URMC, we expect an enrollment rate of ~60%.

- The number of symptomatic AF patients (persistent or paroxysmal) treated by electrical cardioversion at the University of Rochester Medical Center has been in the order of 120 patients per year. We will enroll ~210 subjects (from a pool of 350 patients) during the study period of 35 months.
- There are ~60 symptomatic patients treated by ablation techniques every year at URMC. We intent to enroll~105 of these subjects (from a pool of 175 patients) during the study period of 35 months.
- Because of the relative shortness of the actual study period (2 weeks), we project a potential subject withdrawal rate (by the subject or via subject non-compliance to protocol) at less than 1%. Therefore, subject withdrawal should not require an increase in the projected subject enrollment numbers.
  Hence, we will enroll 315 patients and expect to get ~284 patients successfully converted (90% of the cohort, see Table 1).

	AF Patients	Study Pool	Enrolled (60%)	Converted (90%)	ERAF	NO ERAF
	12 months	35 months				
Ablation Pts	60	175	105	95	38 (40%)	57
Cardioversion Pts	120	350	210	189	57 (30%)	132
		Total	315	284	95	189

Table 1: Table describing the estimated number of patients treated by ablation or electrical cardioversion who are available at the URMC clinic per year (column 1), during the overall time of the study enrollment period (column 2), enrolled in the study (column 3), successfully converted (column 4) and ultimately experiencing ERAF (column 5).

3.1.2 Gender and Age of subjects:

We will enroll adult patients only. AF is a disease that is usually not observed in children and teenagers. The prevalence rates of atrial fibrillation are higher in men compared with women in both the United States and globally. In the largest cotemporary cohort of almost 18,000 patients in the United States, AF prevalence was approximately 30% higher in men as compared to women. These prevalence differences were even more pronounced when looking at global burden of atrial fibrillation. In 2010, global prevalence rates (per 100,000 population) were 569.5 in men and 359.9 in women. The prevalence rates of atrial fibrillation are higher in men than in women in every age group and study enrollment would be expected to reflect these gender specific differences.

3.1.3 Racial and Ethnic origin:

The distribution of races and ethnics will be representative of the pool of patients with AF in Rochester community. We present in Table 2, the estimated distribution for the cohort of 315 subjects

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	10	10	20

Not Hispanic or Latino	89	206	295
Ethnic Category: Total of All Subjects *	99	216	315
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	3	4	7
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	19	19	38
White	73	197	270
Racial Categories: Total of All Subjects *	95	220	315

Table 2: Distribution of races and ethnics in the proposed cohort of AF patient enrolled in our project.

3.2 Inclusion and exclusion criteria

3.2.1 Inclusion criteria:

- Men and women older than 18 years of age,
- Medically-managed for symptomatic AF (persistent or paroxysmal),
- In sinus rhythm after their ablation procedure,
- In sinus rhythm after trans-thoracic electrical cardioversion.

3.2.2 Study Exclusion criteria:

- Implanted with a device (pacemaker, CRT, ICD) and a ventricular pacing requirement superior or equal to 70%,
- Known allergic reaction to adhesives or hydrogels or with a family history of adhesive skin allergies,
- Unable to cooperate with the protocol due to dementia, psychological, or other related reason,
- Refusing to sign the consent for participation,
- Unable to operate the device such as blind patients.
- Patients with Parkinson disease (or other central nervous system disorder/Tremor) who cannot record a stable video signal of their face.
- The subject was previously enrolled in the current study.
- The subject wears clothing covering the face, or uses facial makeup that will interfere with the quality of facial recordings.
- Subject does not have internet access at home and lacks the technology to participate.

3.2.3 Discussion of subject population:

The electrical cardioversion is a procedure that is not used in pregnant women; therefore we do not expect to enroll pregnant women in the AF arm of the study, i.e., patients prescribed with electrical cardioversion.

3.2.4 Vulnerable subjects

For University of Rochester employees who may be approached to participate as subjects in this project: Taking part in this research will not be considered as a part of their University duties, and refusing to participate will not affect their job(s). They will not be offered or receive any special job-related consideration if they take part in this research.

4. SUBJECT IDENTIFICATION , RECRUITEMENT AND CONSENT

4.1 Methods of Subject Identification and Recruitment

The study population will be drawn from the pool of AF patients prescribed with ablation and cardioversion at the University of Rochester Medical Center (Rochester, NY). The patients will be identified by a research staff member who will review the list of patients scheduled for either electrical cardioversion or AF ablation at the URMC (cardiology). Cardiac patients identified during a scheduled clinic visit will be given the option of taking the consent form home to review. Prior to returning to the University of Rochester Medical Center for their procedure (ablation/cardioversion), patients may be contacted by phone (by a research staff member, using the study's approved Oral Script) to assess their interest in participating in the project (given their understanding that they subsequently meet project inclusion criteria after their procedure), as well as specific questions regarding previous computer experience and internet access at home.

4.2 Process of consent

The consent forms will be subsequently signed by the patient, if the patient is still willing to be involved and meet the inclusion criteria of the study as described above. The project consent forms will be stored in specific folders in the secure clinic confidential material file room, and managed by a research staff member. On a weekly basis, the stack of consent forms will be delivered to the HRFUP ECG Core laboratory for storage in the HRFUP secured filing room. A copy of the signed consent forms will be provided to the enrolled patients. Co-investigator, Jean-Philippe Couderc, PhD (Cardiology, URMC) will not consent subjects

5. METHODS AND STUDY PROCEDURE

We will provide a Samsung Tablet (Tab III) or an iPad Pro to the enrolled subjects before they are released from the hospital. Mobile technology is used ~3 hours per day on average, and we will use this time spent on the device to capture VPG signals. Indeed, our software application, when installed on a tablet, can run in the background. The application will automatically be triggered when the subject switches on the device and during various allowable activities performed with the device. The use of the tablet will be limited to watching videos, and accessing YouTube as well as a variety of other public websites. The type of applications (APPs) available to the subject will slightly differ between devices (iPad and Samsung TAB). This recording concept will provide previously unattainable streams of data, with no limit in recording duration and number of recording sessions, to analyze pulse variability and identify the presence of atrial fibrillation. To protect subject's privacy, the access to the email software will be password protected using a password known only by the subject. Furthermore, the subject will be trained to know how to delete the browsing history and cookies from the tablet browser before he/she return the device with the video recordings. Password protection for accessing the Tablet itself would be problematic since it would have to change with every new subject using the device. In addition, the sophistication of the facial recognition software utilized in the study allows the filtering out of images of individuals other than the subject, and, therefore, effectively nullifies the need for the password protection.

The enrolled subjects will be asked to record facial and finger videos for at least 30 seconds : 1) twice a day during a period of 14 days following their procedure, 2) when they feel AF symptoms (~33% should experience symptomatic ERAF), and 3) prior to hospital discharge for the purpose of establishing a baseline recording during sinus rhythm (30 second period). Importantly, before the subjects' hospital release, they will be trained by a research staff member regarding EKG Patch attachment and maintenance; how to operate the tablet VPG, Symptoms, and general applications; and how to obtain technical support during the study period . The subject will subsequently participate in a Pre-Study survey regarding the quality of the training, retention aspects of the training, and their understanding of study support that will be available for them. The subject will be asked the questions in Part A and Part B of the survey by study staff prior to the subjects return to home. The subject will be called by a member of our team within 24-48 hours following their return home from the hospital to ask the remaining Pre-Study survey questions (Part C.), and to verify that the Tablet could be connected to their home WIFI system. If they were unable to connect the tablet, technical support (by the

Project IT manager) will be provided via telephone to assist the subjects in establishing the connection. Subjects may also be contacted by a project team member at 7 and 11 days into their study period to support subject compliance, and to answer any questions the subject may have regarding the study technology. On the last day of their study period (day 14) the subjects will again be contacted by a member of our team to go over any questions the subject may have regarding their EKG Patch removal and the shipping of the patch and the tablet back to the Study Center (the ECG Core Laboratory at the Heart Research Follow-up Program) On or about day 14, subjects will be asked to participate in a Post-Study survey that assesses their general satisfaction and experiences with the study, its staff, and the technology utilized in the study. The survey will be administered to the subject by study staff over the phone. Within 2-weeks of completion of their study period, subjects will be sent a "Thank You" letter from the PI, thanking them for their participation in the study.

5.1 Efficacy Assessment of the proposed technology

To get a reliable reference for confirming the presence of AF, we opted to use the Zio XT® ECG Patch (iRhythm Technologies, San Francisco, CA) in our project. iRhythm developed a patch sensor to record one-lead surface ECG continuously for a period of ~14 days. A growing number of studies demonstrated the effectiveness of this device in monitoring patient for AF burden[16-19]. After the recording period is completed, the patch is mailed to iRhythm for semi-automatic analysis using the ZEUS system (Zio ECG Analysis Services) that combines cloud-based technology and cardiac technician review. In this work, we need to access the raw ECG signal in order to manually adjudicate the ECG rhythm and reliably define the onset and offset of AF episodes across the 14 days. We contacted iRhythm, and arranged that this company share the full raw ECG signals from their patch with our institution to conduct the proposed research work (see letter of support from iRhythm technologies, Zio unit price is ~$260). The 14-day recordings will be cut into 14 signals of 24-hour length and reviewed using standard Holter approach (Global Instrumentation M12A Holter scanning system that utilizes input ECG waveform data in the ISHNE format[21]). These recordings will then be manually adjudicated utilizing the THEW Viewer/Annotator technology developed in our laboratory for 24-hour ECG review (technology used daily in the THEW initiative[20]). Importantly, we will define a clinically-relevant AF episode as a continuously-recorded AF rhythm lasting for a minimum of 5 minutes. Bringing monitoring technologies into the home introduces a series of technical and logistical challenges we discuss in the following sections:

Ensuring usability of the monitoring devices and high quality of recorded data are crucial to the success of this project:

- *Zio XT® ECG patch*: the usability of the patch and the quality of the ECG recording are of no concern in our study because this device is already a fully validated clinical device. From a logistic point of view, the subject will start wearing the patch before s/he leaves the hospital. The patch is placed on the flattest part of the upper left chest, its location is defined using 1 finger width below the collarbone, centered over the left pectoral muscle with the edge of the ZIO Patch next to the sternum, and with an angle so that the arrow on the top patch label points upward. It is important to avoid armpit and breast tissue. There is no activity restriction when the subject wears the ECG patch. The subject will receive a package to mail both the tablet and the patch at the end of the monitoring period (14 days) to the ECG Core Laboratory (ECL) of the Heart Research Follow-up Program. The ECL will 1) load the VPG data from the tablet for processing and 2) will mail the patch to iRhythm for analysis and ECG signal extraction. This data will be available electronically to the ECL using a secured BOX™ server (cloud technology already used by the HRFUP in several FDA-regulated clinical trials).
- *The iPad and Samsung TAB III tablet*: the tablet will provide the following functionalities: *1) VPG monitoring during the time the tablet is used, and 2) a symptom reporting APP that needs to be triggered by the subject if he/she feels AF symptoms, and 3) a Notification APP that will be automatically triggered to insure subject compliance to the protocol.*
    - VPG monitoring:

The tablet will automatically acquire the facial video of the subject when it is in use. Subjects will be asked to utilize the tablet a minimum of 5 minutes, twice a day (in addition to scheduled and symptomatic recordings). The tablet will record successive 30 sec. facial video recordings, extract the information from the video, and send the data to a secured cloud-server (BOX.com). A single picture of the face of the subject will be extracted from the video (at the beginning of each 30sec. recording). This image will be encrypted and sent with the

pulsatile data to the cloud server. Video will then be deleted from the device's hard drive. Subjects will also be required to perform a VPG of his/her face and finger twice daily (with 6 hours between VPGs). The recording of the subject's finger uses the Tablet's flashlight feature through the camera lens on the back of the Tablet to obtain pulse information via the light passing around and through their index finger, and involves little or no risk. The procedure is similar to standard finger pulse oximetry used in hospitals as well in personal use with new wearable devices for measuring oxygen saturation levels and pulse.

- Symptoms APP: Common symptoms often associated with AF are reviewed with the subject by the study nurse as part of the subject's enrollment process and training.
  When the subject feels any of these AF symptoms, she/he will run the SYMPTOMS APP on the tablet that will require the user to respond to the following questions related to AF symptoms:
  SELECT SYMPTOMS THAT YOU ARE CURRENTLY EXPERIENCING:
  - Palpitations (feeling that your heart is skipping a beat, fluttering, or beating too hard or fast)
  - Shortness of Breath
  - Chest Pain
  - Dizziness, Fainting (loss of consciousness)
  - Confusion
  - Fatigue (tiredness)
  - Sporadic Flushing In the Face
  - Feelings of fear or anxiousness.

  After entering the responses, the subject presses the application's Submit Button and, if the subject selected any of the first five symptoms, the following "seek medical attention recommendation" will appear:

  "You have noted that you are experiencing one or more of the major symptoms listed. It is recommended that you call your doctor or seek other medical attention to help relieve your symptoms and possibly prevent further medical complications."

  The subject then must perform two recording sessions of 30sec each. First, a facial VPG followed by a finger VPG recording.
- Notification APP: This APP will run in the background and monitor whether a subject has performed the twice per day VPG of his/her face and finger. To insure that the subject has performed the twice per day VPG recordings, the tablet's Notification APP will notify the subjects up to four times a day (8am, 12pm, 4pm, & 8pm) that a recording is needed to comply to the twice per day recording protocol. If the subject has not performed the task, the APP will provide a verbal message informing the subject that the recordings should be done and to: "Please select OK to take a video". If the subject selects "OK", then the Tablet provides additional verbal instructions on taking the videos and synchronize them with the ECG Patch recording.

  When the facial video is completed, the system will then inform the subject that the facial video is done, and that a video of the subject's finger is to be performed by a light shining through the camera lens located on the back of the Tablet:

  "**Thank you, your facial video is done."**
  "**Please use the camera lens on the back of the Tablet to now perform a video of your index finger. Please do not remove your finger until the light goes out**."

  The subject will then turn the tablet over and place his/her index finger on the camera lens located on the back of the Tablet, and a light will turn on and shine on the subject's finger. The subject will be required to let his/her finger remain in that position until the light goes out.

  When the video is completed the Tablet will go back to the previous screen in use by the subject.

The Notification APP will continue to run in the background and perform its notification process (as described above). The APP will notify the subject up to four times a day (8am, 12pm, 4pm, & 8pm) that a video recording should be done.

The tablets will be setup so the user cannot download and install novel applications that may interfere with the VPG program or/and critically reduce the storage space of the device. Compliancy of the subject with the study protocol will be verified by checking the flow of data onto the cloud server by study staff on a daily basis. Video quality will be qualified using facial detection and other metrics that measure the level of motion of the face in terms of horizontal and vertical axes (expressed in pixels) and analysis of power spectrum. A study research staff member will contact the subject when less than 2 recordings are recorded and sent to the cloud server on a daily basis (we will exclude recordings done by other individuals using the device). A correction plan will be developed on a case-by-case basis. Subjects not having internet home access will not be enrolled in the study.

Subject training: The patients will be contacted by phone and asked to be enrolled in the study prior to their admission to the hospital. When enrolled, and while waiting (45-60 minutes) for their procedure in a private exam room, a research staff member will spend ~ 30 minutes with the subject before their procedure: 1) to describe how to use the personal computer and the embedded applications for the video recordings; 2) to teach the subject to recognize a set of AF symptoms that should alert him/her to record additional VPGs; and 3) to provide contact information for technical support (by the Project IT Manager) in case subject has difficulty using the device. The tablet will also be loaded with training videos/materials available from the tablet's start screen. The subjects will be taught to recognize the AF symptoms (described above) and will be asked to record a facial and finger VPG during those symptoms. A study website (containing the training materials and videos) is available only for subject use through the THEW main website at http://thew-project.org/camafib/index.php.

At the end of the 14-day period, the subject is asked to remove the ECG patch using the procedure described during enrolment (also a video demonstrating the procedure will be available on the tablet). Insert the patch with the Tablet in the provided box, and mail the box to the ECG Core Laboratory (ECL) at the Heart Research Follow-up program.

5.2 Cost to the Subject
There will be no cost to subject for their participation in this study.

5.3 Payment for Participation
Finally, as an incentive for patients to enroll in the study, we will offer the subjects who complete the 14-day follow-up period a payment of $100 (per check mailed to their home address). If a subject withdraws from the study, no study incentive will be paid.

5.4 Project Time Frame
We propose to conduct this project over 8 semesters (S1 to S8) from 2/1/2017 to 1/30/2021. The timeframe will be as follows: study setup, software integration to tablets (S1); subject enrollment for the learning (S2-S4) and validation (S5-S7) datasets; refinement of the AF detection method (S3-S7); validation and publications (S8).

	Timeframe (months)	S1	S2	S3	S4	S5	S6	S7	S8
Study setup	6	■							
Enrollment (learning set)	17.5		■	■	■				
Enrollment (validation set)	17.5					■	■	■	
Data quality monitoring	35		■	■	■	■	■	■	
Develop AF detection method	30			■	■	■	■	■	
Validate AF detection method	3								■
Publications	3								■

Table 3: Time frame of the proposed project over a period of 4 years (8 semesters: S1 to S8).

6. RISK/BENEFITS:

This is a minimal risk study. The ZIO® XT Patch could cause irritation such as redness, severe itching or allergic symptoms (i.e. hives). Identifiable facial images could result in a breach of confidentiality (addressed above). If skin irritation such as severe redness, itching or allergic symptoms develop and persist during the recording period, the subject should remove the ECG patch from their chest and contact the Study Staff (that attached the patch) for any additional instructions/support. The subject will also be encouraged to subsequently advise their primary Care physician that they may have an allergic reaction to medical adhesives. If significant skin irritation persists or if the subject's skin has blistered, they will be advised to seek medical treatment. There is no direct benefit to subjects for their participation. The ECG's will be reviewed by an ECG expert or cardiologist during the following month and the subject will be contacted by Dr. Hall or a member of the study team if the results indicate further follow-up is needed.

7. CONFIDENTIALITY OF DATA AND INFORMATION STORAGE:

We have planned to acquire and analyze one-lead electrocardiograms and video-recordings of subjects' face and finger. The ECG recordings will be associated with subject ID and fully de-identified. There is a potential for data loss/hacking for the facial images going through the web. Although this potential is minimal, we have imposed the following processes to protect the data: The video recordings will be deleted automatically from the tablet after processing and one single image of the face will be kept and associated with the recording measurement. These two pieces of information will be gathered in a single encrypted file. This file will be stored on the tablet and transmitted to a cloud server (BOX.com) using encryption schemes. Therefore, the data recorded with the Tablet are encrypted and moved and stored using devices that are password-protected in order to secure the subject privacy. Data access will be granted only to the individuals involved in the project. The HIPAA requirements around the video data were already addressed when we designed and conducted the study described in the preliminary results.[7] The requirements include specific enrollment and consent forms that describe precisely to the patients how their data will be used, and which organizations will have access to them for research purpose.

Data will be stored in a secure server at the University of Rochester with access limited to study personnel. The cloud server used to host the 30-sec recordings is a Box.com server that is password protected.

Importantly, the facial video images will not be shared with the other organizations (outside of the URMC) in this study in order to protect the privacy of the study subjects. Signals without personally identifying information (VPG only) will be shared with the study collaborators (RIT). All data will be de-identified by URMC to comply with the HIPAA "Safe Harbor" method of de-identification set forth at 45 CFR 164.514(b) prior to disclosure to RIT's investigator. Signed consent forms will be stored in a locked file cabinet with access limited to study personnel. Data will be stored indefinitely.

8. DATA ANALYSIS AND MONITORING

8.1 Power and Sample Size Considerations

In absence of good information on the dependence between the binary AF outcomes over time, we will very conservatively base our power calculations on just one measurement per patient. It is expected that about 35% of patients will experience at least one episode of symptomatic AF within the 2-week follow-up period, while we also expect to capture the occasional asymptomatic AF with the twice daily monitoring. We will thus assume that 35-65% of patients will be in AF at some point during follow-up. Thus of the 142 patients in the Validation Data, we expect 50-92 (but closer to 50) patients to contribute to the estimate of sensitivity, and similarly 50-92 (but closer to 92) patients to contribute to the estimate of specificity. Assuming the true sensitivity (and specificity) is 85%, 50-92 patients in AF provide 75-96% power to reject the null hypothesis that sensitivity ≤

70% using a 1-sided 0.05 level exact binomial test, and similarly for specificity. The power for our planned test based on not just one but all 29 measures for each patient will be higher, especially for testing specificity since the proportion of the 4K measurement times in AF will likely be far less than the proportion of the 142 subjects ever in AF.

8.2 Implementation of the Learning and Validation steps

It is important to note that during the Validation phase of the project, Dr. Jean-Philippe Couderc PhD, MBA will be excluded from evaluating the performance of the VPG technology because of the potential for a conflict of interest. His role during this phase of the project will be that of a technical consultant only. In addition, for the validation phase, blinded study data will be sent to RIT for processing and the results will be sent to Dr. Derick Peterson (U of R) for evaluating the performance of the tested technology to detect the presence of AF. Dr. Peterson, Department of Biostatistics, will be responsible for the statistical analysis of the clinical data at the UR.

-AIM1, Detection Performance of VPG: To address Aim 1 we will use the Training Data) to construct a classifier to predict AF as a function of facial VPG measures, then we will use the Validation Data to provide an unbiased characterization of its performance on independent subjects. Each subject will record a baseline VPG during sinus rhythm. During the 2-week follow-up period, subjects will be asked to record a video selfie (VPG) twice per day, each synchronized with the ECG recording from the Zio patch. Subjects will be asked to perform additional VPG recordings any time they feel symptomatic. The longitudinal binary outcome at each follow-up time will be AF as determined by ECG. We expect to have a minimum of 29 outcomes per patient (2 weeks x 7 days/week x 2 recordings/day + 1 baseline) x 142 patients (half of the 315 enrolled x 90% converted) = 4K outcomes in the Training Data (and similarly in the Validation Data), each with an associated VPG from which the 8 VPG measures described above (PR, heart rate, RMSSD, SDRR, pNN50, SD1, SD2, AFEvidence) will be calculated.

A working independence-based logistic GEE (Generalized Estimating Equations) model will be used to construct the classifier, essentially ignoring any potential dependencies between the longitudinal AF outcomes. We will relax the common assumption of linearity in the logit by considering piecewise constant (or piecewise linear) splines with knots at the quartiles (or tertiles) of each VPG measure, resulting in 3 candidate basis functions per VPG measure (for a total of 24 candidate VPG basis functions). All-subsets and stepwise model selection procedures will be used to select a subset of the VPG basis functions, though the indicator for subject type will be included in all models. Five-fold cross-validation (at the *subject* level, each time omitting all observations on 28 of the 142 Training subjects to maintain independence) may be used to help select the nominal significance level, or model size, as well as the threshold necessary to form the logistic classifier. We will consider relaxing the assumption of additivity by further allowing 2-way interactions between pairs of nominally significant VPG measures.

Once we have selected the VPG measures, their functional forms, any interactions, and a threshold for the resulting linear predictor –as well as completed the Training phase for Aim 2 (as noted below)– all using only the Training Data, we will finally use the independent Validation Data to characterize the performance of the resulting classifier, free of model selection bias. Sensitivity and specificity will be empirically estimated by the marginal mean of the indicators, weighting each of the 4K observations equally, with inference based on robust sandwich covariance estimators accounting for potential dependencies between the multiple outcome measures from each subject. Alternatively, we will first compute subject-specific estimates of sensitivity and specificity, and then average these over independent subjects, thus weighting each subject (rather than each measurement) equally. We will construct robust 90% two-sided confidence intervals (CI) for the sensitivity and specificity, since we are primarily interested in the 95% lower confidence bounds. Although hypothesis tests are of less interest than the point estimates and CI, since the choice of null hypothesis is somewhat arbitrary here, we plan to test the alternatives that sensitivity >70% and specificity >70% (hoping for at least 85%), using 1-sided 0.05 level tests for each. Thus, e.g. if the 90% two-sided CI for sensitivity is fully contained with 0.7-1.0, we will reject the null hypothesis that sensitivity ≤ 70% at the 0.05 level.

We will also construct ROC curves based on the Validation Data to display the trade-off between sensitivity and specificity as a function of the threshold for the linear predictor, and we will compare these to cross-validation-based (as well as optimistic naïve) ROC curves based on the Training Data. To investigate calibration, we will fit a marginal logistic model to the Validation Data with the un-thresholded linear predictor as the sole predictor. Testing the null hypothesis that the slope in this model is 0 tests whether the model is useless, and thus we hope and expect to strongly reject this null hypothesis with a tiny p-value; testing the null hypothesis that the slope is 1 is a test of calibration, and we hope that we fail to reject this null hypothesis with a large p-value (indicating good calibration). We will also use the Validation Data to re-estimate all of the individual coefficients in the marginal logistic regression model, for comparison with the potentially biased estimates from the Training Data.

-AIM2: Benefit of using Baseline VPG Recording: Each subject will have a baseline VPG recorded during sinus rhythm (using the Samsung Tablet). This recording will be acquired after successful procedure and before the subject leaves the hospital. Sinus rhythm will be checked by health professional. To address Aim 2, we will repeat the above general procedure but based on the *differences* from baseline in VPG measures and/or by including the baseline VPG measures along with the instantaneous VPG measures for predicting AF at each time point. When the time comes to open the Validation Data, we will compare the sensitivity and specificity of the classifier from Aim 2 to that of Aim 1 to quantify the potential improvement due to incorporating a baseline VPG.

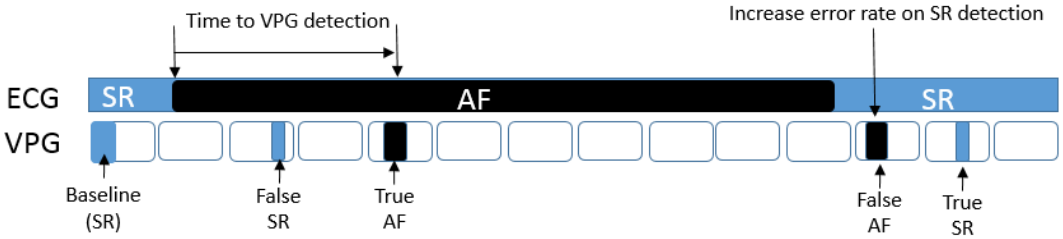

Figure 7: Schematic presentation illustrating the true and false detection of AF and SR rhythm during the 14-day follow-up period of the study. The upper line represents the continuous ECG recording (either blue or black for SR and AF, respectively), while the lower line presents the same 14-day period during which VPG will be recorded. The VPG monitoring periods in which 5 recording sessions are marked (limited to 5 for clarity purpose). We will have at least 2 recording sessions per day, i.e., 28 recordings sessions.

-AIM3: Time delay in AF detection:
We will estimate the sensitivity of the resulting technique as a function of the elapsed time *t* since initiation of AF, which is fundamentally different from the instantaneous sensitivity targeted in Aims 1-2. Since the time of AF will fall randomly within the monitoring period for the ~50 AF patients (half of the estimated ~95 ERAF in Table 1), this will induce right-censoring of the time from first onset of AF (as detected via ECG) until the first true AF detection by VPG, as some patients will only have 1 day of post-AF follow-up while others might have 10 days of post-AF follow-up. Thus, the Kaplan-Meier estimator will be used to estimate sensitivity(*t*), and pointwise confidence bounds will be based on Greenwood's formula for the variance. It should be noted that patients can move out of and possibly back into AF (as measured by ECG) repeatedly over time. If VPG falsely detects AF while the patient is in sinus rhythm (according to ECG), such false detection of AF by VPG will not be counted (see Figure 7). Only true AF detection by VPG, when the patient is in AF (as measured by ECG), will meet the endpoint definition. Thus, if a patient were to quickly resolve from initial AF to sinus rhythm then the sensitivity of the VPG monitoring process would be penalized as it will be impossible to detect AF in such a patient via intermittent monitoring, unless s/he were to return to AF and be monitored during that subsequent episode. While sensitivity (*t*=48 hours) is of particular interest, we will estimate the sensitivity curve for all *t* from 0 to up to 14 days, along with pointwise confidence limits. Similarly, we will use the Kaplan-Meier method to estimate the distribution of the time from hospital discharge (in sinus rhythm) until the first false AF detection by VPG. The latter curve will provide an estimated probability of false detection of AF as a function of follow-up time *t*, which can be interpreted as 1 - specificity(*t*) of the VPG monitoring process. Note that once a patient enters AF (as measured by ECG), if VPG were to (correctly) detect AF then such true AF detection would not meet the endpoint definition, and false AF detection by VPG would be impossible until the patient returned to

sinus rhythm. Thus, this specificity(*t*) of the intermittent VPG monitoring process will be inflated by high prevalence and burden of AF, just as sensitivity(*t*) will be reduced by low AF burden. As an alternative characterization, we will censor patients at onset of AF (as measured by ECG) in order to obtain a pure estimate of sensitivity(*t*) during completely AF-free follow-up. For estimating sensitivity(*t*) we could similarly opt to censor patients as soon as they resolve to sinus rhythm, in order to get a pure estimate of sensitivity(*t*) during the first contiguous period of AF (as measured by ECG). However, we prefer the more conservative estimator of sensitivity(*t*) that penalizes the intermittent VPG monitoring system for failing to detect transient AF in a timely fashion, whereas we prefer the (also conservative) pure estimator of specificity(*t*) during completely AF-free follow-up.

8.3 Data and Safety Monitoring

On a monthly basis, the PI will routinely review cumulative data throughout the study to ensure subject safety and continued validity/scientific merit.

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