Wisconsin Sleep Cohort Study
Cardiovascular Projects Section
Manual of Operations and Procedures

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Overview of the Cardiovascular Projects Section

The cardiovascular projects section of the Wisconsin Sleep Cohort Study involves data gathering, data entry, and interpretation of well-defined physiometric measures pertaining to the cardiovascular system. These data are comprised mainly of 24-hour ambulatory blood pressure recordings, ankle-brachial index studies, resting 12-lead electrocardiograms, and continuous electrocardiographic measurements recorded during in-lab overnight polysomnography. Future studies are expected to include exercise tolerance testing and carotid ultrasonography (carotid intima-media thickness studies).

I. Policy and Procedure for Electrocardiography

(1) Sleep Lab Procedures and Obtaining the ECG

Bedside 12-lead electrocardiograms (ECGs) are obtained on all sleep study participants who undergo in-lab overnight polysomnography. All ECGs are performed in the sleep lab by UW Hospital ECG technicians using Phillips Medical Systems Tracemaster Xli electrocardiographs.

All ECGs are recorded at a standard paper speed of 25mm/sec and amplitude of 10mm/mV.

As of October 2002, ECG tracings are no longer printed or stored with the subject's medical record number or name[1]. These fields now contain the cohort ID number and name code (first three letters of the last name, first letter of the first name, and the visit number), respectively.

The sleep lab staff are to provide the ECG technician with the floppy diskette to be used in recording the ECG tracing. This disk should remain in the sleep lab after the ECG tracing has been recorded.

After the ECG is completed, a paper copy of the tracing is delivered by the ECG technician to the sleep lab staff who in turn deliver the tracing along with the other sleep study forms to the cohort study offices at 502 North Walnut. After the paper tracings are delivered to the cohort office, the cohort ID number and name code printed on the ECG tracing are checked for accuracy and changed by hand if necessary. Ultimately, the ECGs are placed in a box in the main file room until picked up by the cardiovascular projects staff.

A new ECG disk should be started at the beginning of every month to prevent failure of the ECG disk. The ECG disks can hold approximately 30 tracings but have been known to fail with a lower number of tracings due to limited storage space. The label on the new ECG disk should note the start and end date of the disk's use. Currently, all old ECG disks should remain in the sleep lab office. At a future date, these disks will be moved to the Cohort Study offices for permanent storage.

Backups of all ECG disks are made to a shared network folder after the disk has been completed. (Currently, the backup is at: \\Reviewer\GrassPSGv4\ECG data). All backups are stored in separate

[1] Previously, all ECGs were recorded with medical record numbers and full names and all tracings were added to the hospital system by the ECG technician. This policy was changed to comply with HIPAA regulations governing patient privacy.

subfolders that are named according to start and end date listed on the floppy disk. In the event that a backup needs to be restored to a floppy disk, the files within the subfolder may be transferred, in total[2], to floppy disk.

In the event that a physical copy of an ECG tracing needs to be produced, a new copy may be printed using the storage disk and an ECG machine. An ECG technician will be able to print a duplicate ECG tracing from the correct disk given the Cohort ID number and Name Code printed on the tracing. Additionally, all ECGs from a given disk may be printed at once by an ECG technician if needed.

[2] All files from the subfolder must be transferred to the floppy for the backup to be accessible by the ECG computers and machines.

(2) ECG confirmation and evaluation

All ECG tracings are hand-reviewed for abnormalities prior to data entry and analysis. Computer-based interpretations are not relied on for final diagnosis, although computer calculated intervals and axis may be used in analysis. An initial review by an expert ECG interpreter or physician (KMH) is performed to separate those ECGs that are grossly normal from those that require the review of a cardiologist. This segregation should be based on a skilled interpretation and not the severity codes listed on the ECG.

These segregated abnormal ECGs are then delivered to the study cardiologist for final review and confirmation. All abnormal ECGs that are both reviewed by the cardiologist and stored in the UW Hospital ECG database (tracings done before October 2002) are edited and re-printed from that database by ECG lab staff to be entered into the permanent medical record of the cohort participant*. Copies of these confirmed and edited tracings are then returned to the cohort study offices for data entry and statistical analysis.

**As of October 10, 2002 no sleep study ECGs are submitted to the hospital computer system. Only ECGs acquired before this date are editable according to this procedure.*

At the time of this writing, any interpretations of the ECGs tracings NOT STORED in the hospital Tracemaster system (i.e., those stored only on the ECG disks, all ECGs done after October 10, 2002) will be filed with only the cardiologist's handwritten interpretations. It is important to note that there is only one (1) physical copy of this ECG tracing so great care must be taken to ensure that this copy is not damaged.

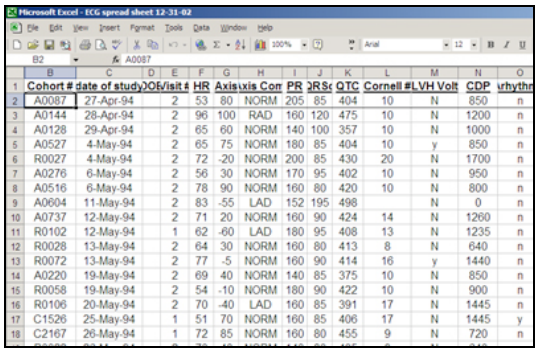
All ECGs performed in the sleep lab up to and including October 1st, 2002 have been confirmed by the study cardiologist. Any ECG performed after that date as of this writing has not yet been confirmed.

In the event that the physical copy of the tracing is damaged or lost, another copy may be printed from the ECG disk using the Tracemaster Xli ECG cart (*see Section 1, Sleep Lab Procedures and Obtaining the ECG*). An ECG technician will be able to assist the sleep lab staff in retrieving any tracings from the disk. **THE ECG DISKS <u>SHOULD NOT</u> BE "DUMPED" INTO THE HOSPITAL TRACEMASTER SYSTEM IN ORDER TO RETREIVE A PHYSICAL COPY OF THE TRACING.**

For answers to any technical questions concerning ECGs or the Tracemaster system, or to get a reprint of an ECG from the disk, contact Joan Bailey, Director of Non-Invasive Cardiology at UWHC.

(3) ECG Analysis, Data Recording, and Organization

All of the data from each ECG tracing are entered into an Excel spreadsheet which is used for subsequent organization and statistical analysis.



Cohort #	date of study	visit #	HR	Axis	xis Corr	PR	QRSd	QTC	Cornell #	LVH Volt	CDP	rhythm
A0087	27-Apr-94	2	53	80	NORM	205	85	404	10	N	850	n
A0144	28-Apr-94	2	96	100	RAD	160	120	475	10	N	1200	n
A0128	29-Apr-94	2	65	60	NORM	140	100	357	10	N	1000	n
A0527	4-May-94	2	65	75	NORM	180	85	404	10	y	850	n
R0027	4-May-94	2	72	-20	NORM	200	85	430	20	N	1700	n
A0276	6-May-94	2	56	30	NORM	170	95	402	10	N	950	n
A0516	6-May-94	2	78	90	NORM	160	80	420	10	N	800	n
A0604	11-May-94	2	83	-55	LAD	152	195	498		N	0	n
A0737	12-May-94	2	71	20	NORM	160	90	424	14	N	1260	n
R0102	12-May-94	1	62	-60	LAD	180	95	408	13	N	1235	n
R0028	13-May-94	2	64	30	NORM	160	80	413	8	N	640	n
R0072	13-May-94	2	77	-5	NORM	160	90	414	16	y	1440	n
A0220	19-May-94	2	69	40	NORM	140	85	375	10	N	850	n
R0058	19-May-94	2	54	-10	NORM	180	90	422	10	N	900	n
R0106	20-May-94	2	70	-40	LAD	160	85	391	17	N	1445	n
C1526	25-May-94	1	51	70	NORM	160	85	406	17	N	1445	y
C2167	26-May-94	1	72	85	NORM	160	80	455	9	N	720	n

These data include all identifying information such as cohort ID, date of study, and visit number, as well as diagnostic data, including wave-intervals (e.g. PR interval, QT interval, QRS duration) and defined diagnosis codes.

The following intervals are calculated by the electrocardiograph and are printed on the ECG tracing in the top-left section of the page:

(1) Rate
(2) PR interval
(3) QRSd (QRS duration in milliseconds)
(4) QT interval
(5) QTc (rate-corrected QT interval)

The following axis information is also calculated automatically by the electrocardiograph:

(1) P-axis
(2) QRS-axis
(3) T-axis

For the purposes of these analyses, the QRS axis is the only axis that is recorded in the spreadsheet.

Determination of axis-deviation is currently automated in the spreadsheet with the following criteria:

(1) LAD (Left Axis Deviation) = QRS axis < -30
(2) RAD (Right Axis Deviation) = QRS axis > 90

Otherwise, the axis is marked as "NORM" indicating a normal QRS axis.

LVH is determined by both the standard voltage criteria, and by the more specific Cornell Voltage Criteria. The Cornell voltage ("Cornell #") must be calculated by hand using the following formula:

Height of R-wave in lead aVL (mm) + depth of S-wave in lead V3 (mm)
Positive if Cornell voltage is $\geq$ 21mm in females, or $\geq$ 28mm in males

The Cornell Duration Product ("CDP") is automatically calculated by the spreadsheet program as the product of the "QRSd" and "Cornell #" entries (*QRSd * Cornell # = CDP*).

All diagnosis codes are organized as arrhythmia, conduction abnormalities, or ischemia. These codes are implemented as a measure of standardization. The codes presently used are derived from the Tracemaster ECG management system and are well known to all UWHC cardiologists. *These diagnostic codes can be found in this manual under Appendix section* ***.

Additionally, dedicated columns exist for left ventricular hypertrophy (LVH, both Cornell Voltage and standard voltage criteria), right ventricular hypertrophy (RVH), and left atrial enlargement (LAE).

(3.1) Data Entry

All diagnostic codes for arrhythmia, ischemia, and conduction abnormalities, regardless of significance, should be entered into the ECG spreadsheet. Determination of significance is made just before analysis, and significance may vary between analyses. For this reason, it is important to include all information regardless of the present importance of the particular finding.

After ECG data has been entered into the spreadsheet, all paper copies of the ECGs are sorted and stored by cohort ID number in filing cabinets for future reference.

It is important to save a new copy of the ECG spreadsheet on each day that the data are updated or edited. Include the current date at the end of each file name (mm/dd/yy) to indicate the different versions. This step is very important if previous analyses are to be revisited. The file name should be similar to the following:

ECG Data Set 07-01-03.xls

It is considered good practice to use this file naming system with all files in the cardiovascular projects section.

(3.2) Current ECG Findings of Interest

The 12-lead ECG is used primarily for the identification of:

(1) Arrhythmia
(2) Ischemia
(3) Conduction Abnormalities

Arrhythmia: Abnormalities of rhythm and rate. Irregular rhythms such as atrial fibrillation, or high-degree atrioventricular block are included, as well as abnormalities of rate, such as tachycardia or bradycardia. Arrhythmia is distinguished from conduction abnormalities in that it affects rhythm, or a change in the focus of initial electrical activation (intrinsic or extrinsic) of the myocardium (e.g., ectopic complexes vs. electronic pacemaker). **Therefore, any abnormality that primarily disrupts rhythm should be considered in this category.**

Ischemia: The Ischemia category of abnormalities is characterized by ST-T wave changes indicative of ischemia or Q-waves indicative of past myocardial infarction (MI). This category also includes non-specific findings that may indicate an "ischemia event" but cannot be clearly identified in the absence of clinical correlation. The name "ischemia" for this category is somewhat misleading, in that the likelihood of identifying active ischemia in this cohort is highly unlikely[3]. ST-T wave changes in active ischemia often resolve very quickly with little to no lasting indication of the ischemic event (in the absence of infarction). To be clear, this category includes all ECG changes that may be derived from an ischemic

[3] This cohort is relatively free of clinically significant cardiovascular disease, and ischemic events most often present with clear symptomology and correlated physiologic response. Active ischemia would most likely be identified and exclude overnight evaluation in the sleep-lab.

event: ST segment changes indicative of recent MI and Q-wave denoting an area of infarction. All indications of ischemia should be reviewed by a cardiologist to rule out primary T-wave abnormalities, abnormalities secondary to LVH, normal early repolarization (anterior ST-elevation), metabolic changes, etc.

Conduction: The conduction category of abnormalities includes those findings which indicate a disruption in the normal conduction pathway in the myocardium. These findings are generally identified by changes in morphology, namely prolongation or acceleration of electrical activation or atrioventricular dissociation. Note that ectopic premature complexes (VPCs or APCs) are not considered conduction abnormalities, but rather arrhythmia because of (1) the change in focus of initial electrical activation and (2) the disruption of rhythm and rate. Conversely, left and right bundle branch blocks, although morphologically similar to intrinsic ectopic electrical activation, do not disrupt rhythm and rate[4] and as such are classified as conduction. *It is beyond the scope of this manual to further elaborate on the identification of conduction abnormalities.*

[4] This is of course not universally true; rhythm and rate may be occasionally disrupted by bundle branch blocks, however elaboration on this pathophysiology is beyond the scope of this text.

II. Policy and Procedure for the Ventricular Premature Complex Study

(1) Overview of Ventricular Premature Complex (VPC) Study

From what is known and can be inferred about the underlying mechanisms of sleep-disordered breathing (SDB) and its acute effects on cardiovascular hemodynamics, there is sufficient reason to suspect that SDB may lead to an increase in ventricular ectopy during sleep and that there would be a dose-response relationship in this association. To assess this possible relationship, we have evaluated several overnight polysomographic studies for evidence of ectopy, looking at both frequency of ventricular premature complexes (VPCs) and the coincidence of this ectopy to abnormal breathing events and sleep state changes.

(2) Evaluation of PSG Records and Interpretation of VPCs

All overnight PSG records include a single ECG rhythm strip that is continuously recorded (paper speed of 10mm/s and amplitude of 30 _V/mm) throughout the entire sleep study.

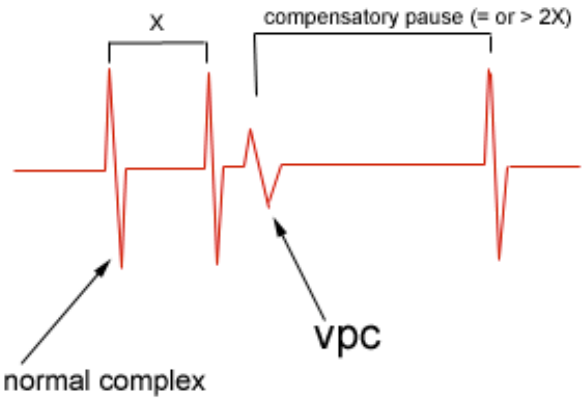


Figure 2: morphology of a VPC; also note that the compensatory pause must be at least double the preceding R-R interval.

As is noted in Figure 2, the morphology of a VPC in this continuous rhythm tracing is generally unique, and **must** be followed by a complete compensatory pause[5].

All VPCs are recorded on sheets with a notation of the page/epoch number and the frequency within that epoch (*see appendix* ***). For example, if more than one VPC is noted, this is recorded as the number of VPCs followed by the epoch number. Each VPC does not need to be recorded separately; a distinction is made only between epochs/pages.

In a subset of these records, after all VPCs were recorded, these data were compared with the sleep score sheet in the cohort participant's master folder to evaluate the coincident occurrence of VPC events and sleep state changes. Considerable sleep state changes in this instance were those where there was some significant change in the state of sleep (greater than three stages), or any sleep stage to wake. Further variables recorded were the sleep stage in which the event occurred, if there was a sleep state change, apnea events, periodic leg movements (PLMS), and other comments. These data were not used in the final analysis due to lacking significance and power.

[5] A true or full compensatory pause is one that is at least double the preceding R-R interval. If this pause is not full, the complex can not be clearly identified as a VPC.

Five or greater VPCs per night of sleep are considered to be significant. Initial findings show, as would be predicted, that the distribution of VPCs is quite skewed; a large majority of volunteers have no VPCs during the sleep study. However, a few (< 1%) have more than 1000 events per night. Not surprisingly, the median number of VPC is zero.

Publications and Writings

THE ASSOCATION BETWEEN SLEEP-DISORDERED BREATHING AND VENTRICULAR PREMATURE COMPLEXES IN THE WISCONSIN SLEEP COHORT STUDY (Original APSS Abstract)

Introduction
Previous studies have shown an association between sleep-disordered breathing (SDB) and cardiac arrhythmias in patients with symptomatic SDB. To date, there has been no study investigating the association of occult SDB with resting electrocardiographically (ECG) indicated ventricular ectopy in the general population. We investigated the association between polysomnographically (PSG) determined SDB and ECG indicated ventricular premature complexes (VPCs) in a population-based sample of middle-aged men and women enrolled in the Wisconsin Sleep Cohort Study.

Methods
We performed a cross-sectional analysis on 352 overnight in-laboratory PSG studies to compare the number of VPCs observed in a subgroup of participants with occult SDB to an age-and sex-matched subgroup of participants with no SDB. SDB status was defined by the apnea-hypopnea index (AHI), the number of apneas and hypopneas per hour of sleep, as a summary measure. Occult SDB was defined as an AHI > 5. Occurrences of VPCs were recorded from a continuous single-lead tracing by trained readers blinded to the participant's SDB status. The relationship between AHI categories (AHI < 5, n=195; AHI 5-30, n=139; AHI $\geq$ 30, n=18) and VPCs was investigated using multiple logistic regression analysis, controlling for age, sex, total sleep time, BMI, history of heart disease, and alcohol and smoking status.

Results
The mean age of study participants was 48 years; 72% were men, 28% women. The overall prevalence of 5 or more VPCs per period of sleep was 15%. The proportion of participants with 5 or more VPCs in each AHI category (AHI < 5, 5-30, > 30) was 13%, 14%, and 44%, respectively. The adjusted odds ratio of 5 or more VPCs for AHI $\geq$ 30 versus AHI < 5 was 6.2 (95% CI, 2.04 – 23.50). The adjusted odds ratio for 5 or more VPCs for AHI 5-30 versus AHI < 5 was 1.1 (95% CI 0.5 – 2.2).

Conclusions
We found a significant association between SDB and VPCs in a subgroup analysis of participants from the Wisconsin Sleep Cohort Study. This association was limited to the moderately severe SDB category of AHI $\geq$ 30. These findings suggest that moderately severe SDB may be a risk factor for cardiac electrical instability, which may predispose to more serious cardiac arrhythmias.