Can an Intensive Approach Improve the Efficiency of Treatment for Patients Admitted for Syncope of Unexplained Etiology?

Steven Jacoby

A. Statement of study rationale and purpose

The inpatient management of unexplained syncope is largely undefined, and broad variations exist in both the use of diagnostic tests and length of stay. This pilot study seeks to help describe the current inpatient syncope work-up and compare it to an expert-driven approach in several measures of quality of care and safety. We will seek to describe the issues that extend the length of stay, and the differences in management strategies between syncope specialists and non-specialists. With this information, we will seek to identify an inpatient diagnostic algorithm and the baseline data that can form the basis for the design of a multicenter randomized controlled clinical trial to test this algorithm.

This study will compare standard care for patients admitted for syncope with an intensive approach. The intensive approach will include a specialist who, as a consultant, will facilitate a more efficacious work-up utilizing the most current techniques. It is hypothesized that the intensive approach will shorten hospital stays and lead to better diagnosis yield, benefiting patient care. The primary objective of this study is to determine if an intensive approach can safely decrease the length of stay for patients admitted with syncope.

B. Background

Syncope, defined as a transient loss of consciousness with spontaneous recovery, is a common reason for admission to the hospital, representing 1-2% of all hospital admissions.[1] A minority of these patients present with obvious causes for syncope, such as a significant gastrointestinal bleed or a clear vasovagal event, some of which require hospitalization for treatment. The majority of patients present with syncopal events of unclear etiology. Although some diagnostic algorithms published in peer reviewed journals exist [1,2,3] there is no consensus on the optimal inpatient work-up of such patients nor the optimal use of the latest diagnostic procedures.

The purpose of the inpatient work-up for syncope of unknown etiology is to evaluate the patient's risk for an arrhythmic etiology. Several therapies, such as implantable defibrillators and pacemakers, have been proven to benefit patients with a high risk for arrythmias or sudden death. Patients shown to have low risk of these adverse outcomes can be discharged without intervention.

Unfortunately, the data available on the current inpatient evaluation imply that physicians do not move gracefully through the risk assessment and the patient with syncope continues to receive a lengthy and uneven work-up from physicians. A retrospective review of a representative sample of adult admissions to Columbia Presbyterian Hospital for syncope in 1995-6 [4] reveals that physicians continue to order inefficient tests, which do not lead to diagnostic progress. Tests with high yields for assessing cardiovascular risk, such as Electrical Programmed Stimulation (EPS) of the heart and T-Wave Alternans, are severely underutilized. Patients are discharged without a diagnosis almost as often as not; the length of stay is inordinately long.

This proposal outlines the implementation of an intensive approach to the syncopal patient. Similar to the dedicated stroke team, activated for patients with acute strokes, and the protocols for rapid risk assessment and management of patients with acute coronary syndrome, both already implemented at Columbia Presbyterian, a "syncope team" may help to optimize the management of patients admitted for syncope of unknown etiology. Although it is intuitive that syncope experts will manage syncope better than non-specialists, it is not clear that the benefits will outweigh the investment required for such a

system. This pilot study will seek to quantify the how much such a team would facilitate the work-up and benefit the patient.

Additionally, the study seeks to develop a straightforward diagnostic algorithm, encapsulating the decision making of the team. This tool could than be prospectively tested, in the form of a critical pathway. A pathway of this type has recently been validated in a multicenter RCT for the management of community-acquired pneumonia.[7] Once validated a clinical guideline may be established. Although a large gap exists between disseminating such guidelines and changing clinical practice, this would represent an important first step,

C. Study Design and Analysis

This study is a single center, prospective clinical trial, with a serial design. In the first part of the study, the usual treatment period, 58 consecutive patients will be enrolled, and baseline data collected in a standard way. These patients will be followed, without active intervention, to assess the primary and secondary outcomes. During the second, or intensive, part of the study, the next 58 patients will be enrolled for active management by specialists. Patients will exit the study after the 12-month follow-up assessment.

All patients admitted by the Columbia-Presbyterian Emergency Room for unexplained syncope will be eligible for enrollment. They must have received an initial work-up conforming to the standard of care, namely history, physical examination, and ECG. Data concerning the reason why any eligible patients did not enroll will be collected.

There will be no strict algorithm for work-up in the intensive management cohort, although general guidelines will probably be developed and revised. Patients will be assessed for their risk for sudden cardiovascular death by a specialist and then appropriate tests will be pursued. Some patient's presentation may be deemed to be already diagnostic for a benign etiology; these patients may have a low cardiovascular risk requiring no further assessment. Others will require testing to quantify their risk and need for interventions.

D. Methods

All patients admitted by the ER for work-up of syncope of unclear etiology would be enrolled in the study and followed prospectively. For the first part of the study, a baseline data collection would be established for "standard care" for 58 patients. In the second part of the study, an intensive management team will facilitate the care of the next group of 58 enrolled patients.

This team will act as a consult service to guide the management of patients and attending physicians will retain ultimate control and responsibility for patient care. Discrepancies between the recommendations of the team and the care of the patient will be noted and described.

Data collected during the hospitalization will include: length of stay; tests utilized during hospitalization (categorized as syncope related or unrelated); and established diagnosis.

Each patient will undergo evaluations at hospital discharge, and 12 months. Data collected in each visit will include information related to any interval syncopal events, arrhythmic events, changes in treatment, syncope-related and -unrelated health care utilization, and measures of satisfaction with the management of their syncope. Each patient will exit the study upon completion of the 12-month assessment.

As a substudy to describe physicians' understanding of cardiovascular risk and the syncopal work-up, during the intensive management period the team specialists, attendings and residents will be asked to rate the patient's cardiovascular risk at different time points.

a. Analysis

The primary endpoint of the study is the length of stay for the syncopal work-up, defined to exclude days spent in the hospital for unrelated intervening complications. The censure of "unrelated days" will be accomplished by consensus of review panel blinded to the group of the patient in question.

An unpaired t-test will be used to compare the length of stay between the two approaches to care. Length of stay data for identical admission diagnosis from pooled data for all of NY State during the time periods included in the study will be analyzed to assure that changes in the climate of care did not effect the analysis.

Survival analysis techniques will be used to analyze the time to a post-discharge arrhythmic event, a syncopal event, or mortality. A Kaplan-Meier product limit method will be used to calculate survival probabilities and log-rank tests will be used to compare the survival curves between the two groups. A similar survival curve analysis will be applied to days in hospital until established diagnosis.

Other secondary comparisons between the two approaches to care will include:

- the utilization of diagnostic tests during the hospitalization and the following year (for syncope related and total health care)

- level of patient satisfaction with their syncope management

Finally, the accuracy of predictions of each patient's level of cardiovascular risk will be analyzed by level of training (resident, attending, syncope specialist).

b. Sample Size

The sample size was determined based on a retrospective review of syncope admissions from 1995-6 at Columbia Presbyterian.[4] For the purposes of the power calculation, the average LOS for the syncopal work-up taken as 3.8 with a standard deviation of 2.3 days. For 80% power to detect a p=0.05 using an unpaired t-test, to detect a difference of 1.5 days between the each of the study arms, each arm should have 58 patients.

E. Study Procedures

The work-up for syncope will proceed along the current standard of care. Identical tests will be available during the standard care period and the intensive management period. These tests will include cardiac (echocardiography, carotid massage, exercise stress test, tilt table test, signal averaged ECG, telemetry, catheterization, electrical programmed stimulation, loop and holter monitors and T-wave alternans) and non-cardiac evaluations (including head CT, EEG, carotid doppler).

F. Study Drugs

There are no study drugs in this protocol.

G. Medical Devices

No new medical devices will be used for this protocol.

H. Study Questionnaires

A short questionnaire will be administered to patients to measure of satisfaction with their inpatient work-up at or shortly after discharge. It will be given again at the end of the study period.

During the intensive management period, after a patient is admitted, physicians treating the patient will be asked to assess a patient's cardiovascular risk on an analog (or visual) scale from low to high risk.

I. Study Subjects

116 adult male and female patients presenting for evaluation of unexplained syncope to Columbia Presbyterian will be enrolled. The patient base of Columbia Presbyterian Hospital should ensure racial, ethnic and gender diversity.

a. Inclusion Criteria

- Etiology of syncope episode is determined to be unknown after initial ER work-up (or as assessed by a private attending in the case of direct admission).
- Completion of medical baseline infon-nation including physical examination, medical history, patient demographics and 12-lead resting ECG.
- Able and willing to comprehend and sign informed consent document.
- Able and willing to participate in scheduled follow-up evaluation at twelve months.
- Age: 18 or older.

b. Exclusion Criteria.

- Likely to survive twelve months of follow (no advanced chronic diseases)

J. Recruitment of Subjects

Subjects will be recruited from patients admitted to Columbia Presbyterian Medical Center with a diagnosis of syncope of unknown etiology by ER physicians. They will be approached for assent by their private physicians, or in the case of ward patients, by housestaff. They will then be consented by a member of the study team within 12 hours of admission.

K. Confidentiality of Study Data

The data obtained from this study will only identify a patient with a numeric identification code. Data files will be entered and stored in a database at Co I umbia- Presbyterian. Results of this study may be used in scientific publications or presentations, but patients' identity will remain confidential.

L. Potential Conflict of Interest

There are no potential conflicts of interest related to this protocol.

M. Location of the Study

This data from this study will be collected in the Syncope Center (Harkness 3), in the inpatient wards of Columbia Presbyterian Medical Center (Milstein Building), and in the diagnostic laboratories utilized in the evaluation of syncope. These laboratories include the Holter Laboratory (Harkness 3), the Tilt Table Laboratory (Harkness 3), the Echocardiography Laboratory (PH 9 Center), and the Electrophysiology Laboratory (Milstein 2HS).

N. Potential Risks

There are no specific risks associated with participating in the study other than the known risks for the specific procedures. The study will be monitored by an independent safety committee and will be halted if a substantial difference in risk is identified prior to completion of the study.

O. Alternatives

The alternative to participating in this protocol is simply not to participate and to have the evaluation of syncope proceed without the guidance of a specialist team. This may involve any of the diagnostic testing modalities available.

P. Compensation to Subjects

There will be no compensation to subjects for participating in this protocol.

Q. Costs to Subjects

There will be no additional costs for a subject to participate in this protocol. All of the diagnostic modalities being utilized in this study are approved, generally accepted, reimbursable diagnostic tests.

R. Minors as Research Subjects

This study will not involve the participation of minors.

S. Radiation or Radioactive Substances

This study will not involve the use of radiation or radioactive substances.

T. Limitations

Although improved better patient clinical outcomes would certainly be the most compelling measure for physicians when assessing the value of an intervention, this study is powered instead for length of stay for two reasons. First, in the population being studied, the events are rare, even in the small number of patients at high risk for arrhythmia and sudden death. Kapoor, et. al. found in their cohort of all patients presenting with syncope to an emergency room, of those with high risk (with 2 or more of the following risk factors: abnormal ECG, history of ventricular arrhythmia or CHF and age >45) 2-14% died in the following year of a cardiac cause. [6] The patients with the highest risk in their study presumably would have been more likely to have a presentation diagnostic for arrhythmia, and would be excluded from the present study, lowering further the expected number of events for this study. Of patients referred to EPS study because of syncope, only 11% had a combined end-point including death, sustained VT/VF or appropriate ICD discharge in the subsequent 12 months.[9] Although it would be possible to study a composite outcome including recurrent syncope, arrhythmia, unexplained falls and death from cardiovascular causes, the study size would probably need to be vast to detect differences; in fact this pilot will help to acquire the data required to make more accurate power calculations.

Second, it is difficult to directly relate improvements in the quality of the diagnostic inpatient work-up for syncope to such hard outcomes as events or mortality. In a study of community-acquired pneumonia, the quality and efficiency of care (including measures such as more rapid initiation of antibiotics) had a clear effect on concrete outcomes such as 30-day mortality. Therefore it was relatively straightforward to test the relationships between quality measures and .30-day mortality.[8] The inefficient timing of an study (e.g. an electrocardiogram) for the inpatient work-up of syncope has a less clear relationship with adverse events.

Although the T-wave alternans test may be emphasized as a powerful non-invasive early test for the **inpatient risk stratification** in the intensive group, this trial is not meant to formally evaluate the tests' sensitivity and specificity for, this population. This study is designed to answer questions about the heterogeneous group of patients admitted by ER physicians for unexplained syncope. For many of these patients a T-Wave Alternans would not be the first test of choice. Limiting the cohort to a group for whom the T-Wave Alternans would be a rational first choice would narrow the general izabi lity of the conclusions about the inpatient management of syncope.

Declaring a diagnosis for a patient with syncope is a complex act, quite unlike the identification of a bacteria from a culture. Most diagnoses are probabilistic in nature. A positive carotid massage may be convincing to establish carotid sinus sensitivity as the diagnosis for a patient in the eyes of one clinician, but not for another. Thus deciding if the inpatient work-up has made a diagnosis will be handled by consensus of a group of experts receiving a summary of the clinical presentation and course.

U. References

[1] Linzer M, et. al. Diagnosing Syncope (Part 1: The value of History, Physical Exam and Electrocardiography. Ann Internal Medicine 1997;126:989-996)

[2] Linzer M. Yang EH. Estes NA 3rd. Wang P. Vorperian VR. Kapoor WN. Diagnosing syncope. Part 2: Unexplained syncope. Annals of Int Med 1997; 127:76-86.

[3] Kapoor WN. Primary Care: Syncope. NEJM 2000;343:1856-61.

[4] Stetson P, Maurer M, Bloomfield DM. Current Diagnostic Testing Patterns in Syncope. Unpublished. [Communication Dr. Bloomfield.]

[5] Gold MR, Bloomfield DM, et al. A Comparison, of T-Wave Altemans, Signal Averaged Electrocardiography and Programmed Ventricular Stimulation for Arrhythmia Risk Stratification. J Am Coll Cardiol 2000;36:2247-53.

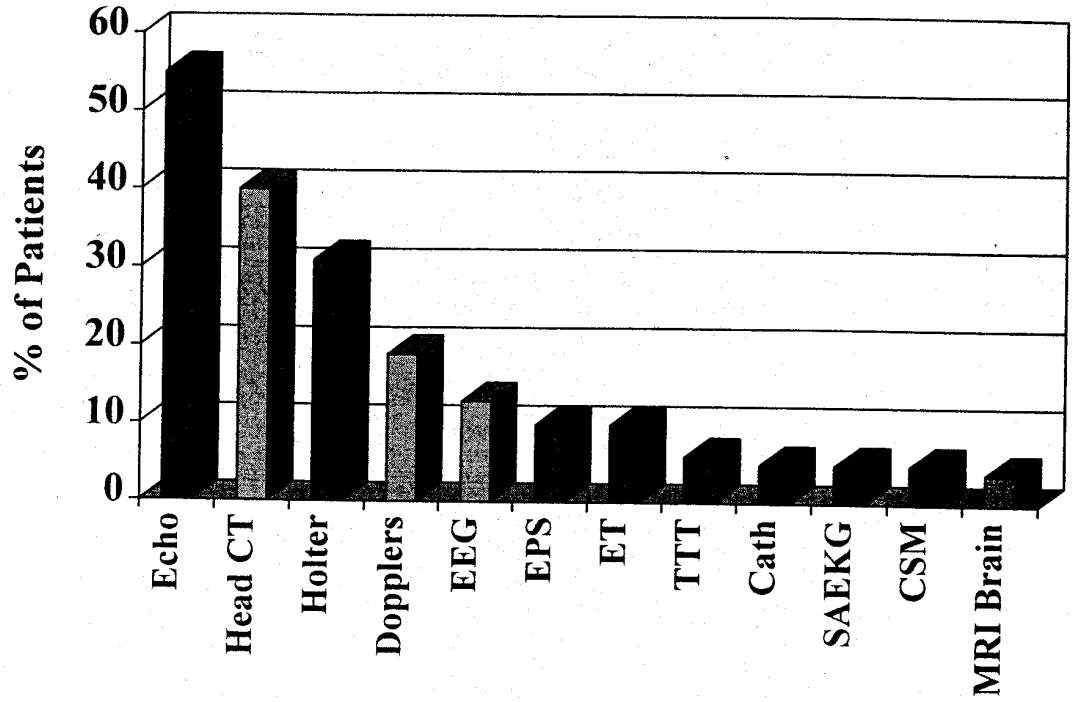
[6] Kapoor WT, et al. Risk Stratification of Patients with Syncope. Annals of Emerg Med 1997;29:459-66.

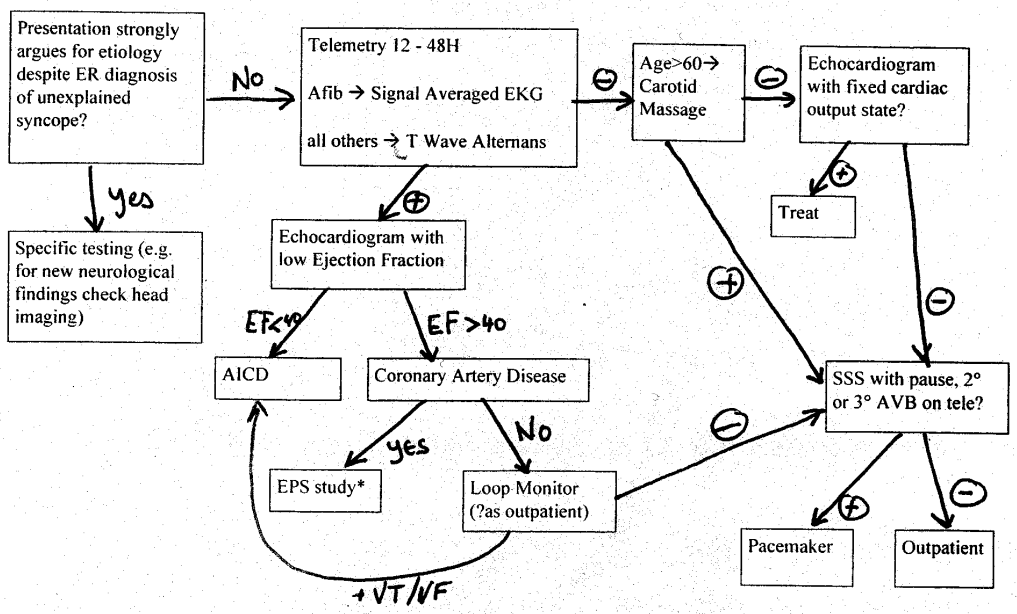
[7] Marrie TJ, et al. A Controlled Trial of A Critical Pathway For Treatment Of Comm un ity-Acqui red Pneumonia. JAMA. 2000;283:749-55

[8] Fine JM, et. al. Quality of Care, Process, and Outcomes in Elderly Patients with Pneumonia. JAMA 1997;278:20802084.

[9] Bloomfield DM, et. al., T-Wave Alternans Predicts Arrhythmic Events in Patients with Syncope Undergoing Electrophysiology Testing. Unpublished [Communication Dr. Bloomfield.]

Utilization of Tests During 100 Admissions for Syncope (1995-6) [4]




Presentation strongly argues for etiology despite ER diagnosis of unexplained syncope?
No
Telemetry 12 - 48H
Afib → Signal Averaged EKG
all others → T Wave Alternans
Age>60→ Carotid Massage
Echocardiogram with fixed cardiac output state?
Treat
yes
Specific testing (e.g. for new neurological findings check head imaging)
Echocardiogram with low Ejection Fraction
EF<40
EF>40
AICD
Coronary Artery Disease
SSS with pause, 2° or 3° AVB on tele?
yes
No
EPS study*
Loop Monitor (?as outpatient)
+VT/VF
Pacemaker
Outpatient
* patients with believed serious CAD may need cath before EPS study