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Electrocardiographic abnormalities in patients with subarachnoid hemorrhage

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Electrocardiographic Abnormalities in Patients with Subarachnoid Hemorrhage

by

Claire E. Sommargren

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

Nursing

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

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Chapter 2:

Chapter 3:

Dedication

This dissertation is dedicated to my husband, Dr. Gary Sommargren, without whose support, love, and inspiration I could not have completed this work.

Acknowledgments

I would like to acknowledge Dr. Barbara Drew, who directed and supervised my research work. Dr. Drew generously shared her invaluable expertise in electrocardiology, provided strong mentorship, and constantly inspired me to reach further. I would also like to acknowledge the support of Dr. Jonathan Zaroff, whose expertise in myocardial dysfunction brought an additional perspective to my dissertation work. I am grateful for the assistance provided by Drs. Robert Warner, Igor Mitrovich, and Steven Paul in their respective fields of cardiology, neurophysiology, and statistics.

Recognition is also due to the team of research assistants who participated in the collection of data for this research: Dr. Nader Banki, Dr. Alexander Kopelnik, Dr. Avinash Kothavale, Dr. Poyee Tung, Landis Fisher, and Jake Miss. I would also like to acknowledge the support and encouragement of the entire research team in the Drew Ischemia Monitoring Laboratory. Last, but not least, this dissertation research would not have been possible without the collaboration and enthusiasm of the nursing staff in the Neurological Intensive Care Unit, who valued and welcomed the research process into their workplace.

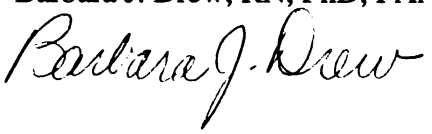
The text of Chapter 2 of this dissertation is a reprint of the material as it appears in the American Journal of Critical Care [Sommargren, C. E. (2002). *American Journal*

of Critical Care, 11, 48-56]. The text of Chapter 3 is a reprint of the material as it appears in the Journal of Electrocardiology [Sommargren, C. E., Zaroff, J. G., Banki, N., Drew, B. J. (2002). Electrocardiographic Repolarization Abnormalities in Subarachnoid Hemorrhage. *Journal of Electrocardiology, 35 (Suppl. 2002),* 257-262]. Permission to reproduce the material has been granted by the copyright owners.

Research Advisor's Statement:

The published material in Chapter 3 is substantially the product of the student's period of study at the University of California, San Francisco and was primarily conducted and written by the student. The pilot study described in the article reports a major finding from the student's doctoral work, and serves as a basis for the research described in subsequent chapters. It meets standards of scientific rigor, and represents research comparable in scope and contribution to the portion of the standard dissertation it replaces.

Barbara J. Drew, RN, PhD, FAAN



Electrocardiographic Abnormalities in Patients with Subarachnoid Hemorrhage

Claire E. Sommargren

Abstract

Subarachnoid hemorrhage (SAH) is a serious neurological disorder in which electrocardiographic (ECG) abnormalities occur in patients without pre-existing cardiac disease. Little is known about the prevalence, timing, and significance of these abnormalities. All prior investigations were limited by incomplete ECG data obtained from either a single or daily ECG tracing or single-lead rhythm strip. This study utilized computer-assisted ECG technologies to collect continuous 12-lead ECG information during the acute phase of illness. This study described the frequency, duration, and timing of ECG abnormalities after SAH, and investigated their relationship with demographic, clinical, and outcomes variables. Results: Analysis of 89,430 12-lead ECGs from 227 patients over a mean monitoring time of 114 hours showed: (1) enhanced atrioventricular nodal conduction in 67%; (2) high QRS voltage in 80%; (3) prolonged QTc interval in 73%; (4) ST segment elevation in 67%; (5) ST segment depression in 50%; (6) T wave inversion in 82%; and (7) abnormal U waves in 20%. Controlling for demographics, risk factors, and disease severity, prolonged QTc interval was an independent predictor of myocardial injury (OR=8; p=0.01), and T wave inversion was predictive of ventricular dysfunction (OR=4.4; p=0.02). Most abnormalities occurred in some proportion of patients on all days studied after SAH (day 2 to day 20). Most abnormalities peaked in frequency later than day 12. Only ST depression at J+60, abnormal U waves, and T2 deflections showed declining frequency later in the clinical course. Maximum durations

of ECG abnormalities ranged from 3.5 days for ST elevation measured at the J point, to 16 days for shortened PR interval. Conclusions: A very high proportion of SAH patients have ECG abnormalities. Enhanced AV nodal conduction and high QRS voltage are suggestive of excessive sympathetic response and high catecholamine levels. ST segment changes that indicate myocardial ischemia in patients with coronary artery disease are not indicative of myocardial injury or dysfunction in SAH patients. However, SAH patients with prolonged QTc intervals are more likely to have myocardial injury and those with T wave inversion are likely to have ventricular dysfunction. Most ECG abnormalities occur later in the clinical course than previously reported.

Barbara J. Drew

Committee Chair

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Chapter 1: Introduction

Subarachnoid hemorrhage (SAH) is a catastrophic neurological disorder than occurs in approximately 30,000 persons annually in the United States REF. It occurs in a younger and generally healthier population than other types of strokes, with a mean age of occurrence of 50 years (Bonita, Beaglehole, & North, 1983; Ingall, Whisnant, Wiebers, & O'Fallon, 1989; Solenski et al., 1995), and it accounts for 41% to 54% of strokes occurring in persons 34 years of age or younger (Gudmundsson & Benedikz, 1977). The mortality rate for SAH has been reported from 30% to 57% (Bamford, Sandercock, Dennis, Burn, & Warlow, 1990; Bonita & Thomson, 1985; Kotila, 1984; Longstreth, Nelson, Koepsell, & van Belle, 1993), and more than 30% of surviving patients are left with some degree of neurological deficit (Ingall et al., 1989).

In addition to the classic signs and symptoms of SAH, which include sudden, severe headache, nausea, vomiting, and nuchal rigidity, ECG abnormalities are frequently reported. The most common of these abnormalities include prolonged QTc interval, ST segment deviation, and T wave inversion. They can bear a striking resemblance to ECG abnormalities associated with myocardial ischemia or infarction. Repeatedly, however, patients with SAH who have exhibited these abnormalities have been proven, by angiography or direct examination at autopsy, to be free of coronary artery disease.

Interpretation of ECG abnormalities associated with SAH as indicating CAD can result in inappropriate management of the patient. Some therapies utilized for cardiac conditions, such as thrombolytic and antianginal agents, are clearly not appropriate for patients with SAH. Misinterpretation can result in delay in instituting therapies needed

for effective management of SAH, as well as refusal of donor hearts from patients with SAH dying from brain death, because of the mistaken belief that the patient has CAD.

Etiology

A number of etiological theories have been proposed for the occurrence of ECG abnormalities associated with SAH. Several, such as CAD, coronary artery spasm, and electrolyte disturbances, have been generally contradicted by a body of research findings (Chang, Lee, Hung, Kaun, & Cheng, 1998; Cropp & Manning, 1960; Rudehill, Olsson, Sundqvist, & Gordon, 1987; Yasu, Owa, Omura, Katsuki, & Saito, 1993). Increasingly, evidence is mounting in favor of a neurogenic hypothesis for the generation of ECG abnormalities after SAH. Findings from numerous well-controlled investigations of neurological factors, particularly focusing on the sympathetic division of the autonomic nervous system, have supported this theory (Klouda & Brynjolfsson, 1969; Kralios, Martin, Burgess, & Millar, 1975; Rogers, Abildskov, & Preston, 1973).

Drislane. Samuels, Kozakewich, Schoen, and Strunk (1987) proposed the catecholamine hypothesis (Figure 1) in which the body is subjected to a surge of sympathetic outflow, resulting in ECG abnormalities and other cardiac effects. The presence of blood, and subsequent increased intracranial pressure, in the vicinity of the hypothalamus, is a suspected source of stimulation of excessive sympathetic outflow after SAH (Cruickshank, Neil-Dwyer, & Stott, 1974b). This results in local catecholamine release from the intracardiac sympathetic nerves, as well as an increase in circulating catecholamines. Investigators have described scattered areas of microscopic myocardial injury, called contraction band necroses, focused near the intracardiac sympathetic nerve endings in patients with SAH (Greenhoot & Reichenbach, 1969). These cardiac lesions

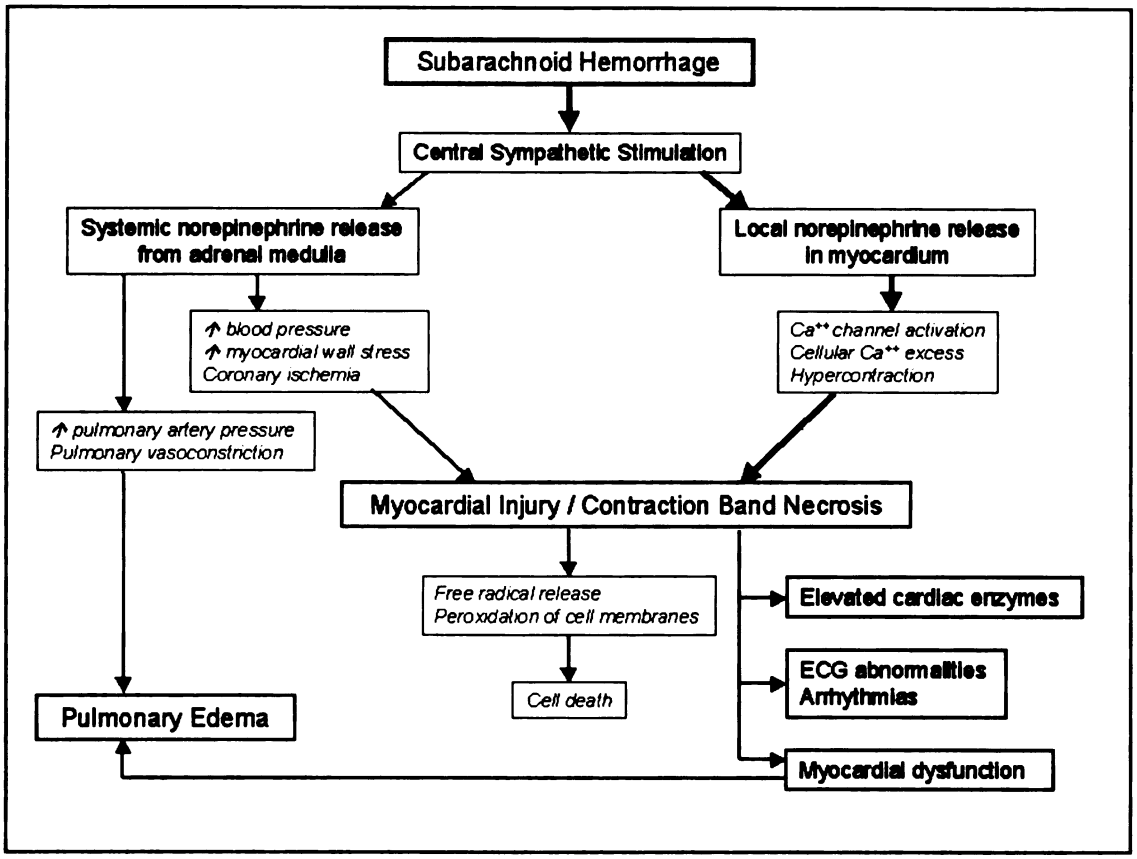

Figure 1. The catecholamine hypothesis for development of ECG abnormalities and other cardiac phenomena after subarachnoid hemorrhage.

may cause elevated serum cardiac troponin I, a biomarker of myocardial injury, and prolong the repolarization of the myocardium as the wavefront progressions is slowed by areas of necrosis scattered throughout the myocardium. (Drislane, Samuels, Kozakewich, Schoen, & Strunk, 1987; Parekh et al., 2000).

Excessive outflow from the sympathetic nervous system has also been hypothesized to cause myocardial wall motion abnormalities (Zaroff, Rordorf, Ogilvy, & Picard, 2000) and pulmonary edema in the setting of SAH (Mayer et al., 1994).

Prevalence, Timing, Duration, and Clinical Implications

While there have been numerous studies of the prevalence of ECG abnormalities occurring after SAH, many questions remain unanswered. Reported prevalences vary widely, which may be due to differences in study design, frequency and timing of ECG tracings, and definitions of ECG abnormalities. Very little research has been conducted to determine the timing and duration of these ECG changes. Studies have generally not monitored patients consistently or over a substantial period of time. Many relied on a one or a few ECG tracings, and those utilizing serial ECG recording most often did not report timing or duration.

There have been conflicting reports of the clinical implications of ECG abnormalties after SAH, and their relationship to morbidity and mortality has not been clearly established. While several investigators found that ECG changes were a poor prognostic sign (Cruickshank, Neil-Dwyer, & Brice, 1974a; Galloon, Rees, Briscoe, Davies, & Kilpatrick, 1972), this has not been consistent. Zaroff and colleagues found that ECG abnormalities were not significantly related to mortality.

Dissertation Aims

The goal of this dissertation research was to determine the prevalence of ECG abnormalities in patients with SAH, the timing and duration in the clinical course of these changes, as well as their relationship to demographics, risk factors, disease severity, and outcomes. The use of continuous 12-lead ECG monitoring allowed collection of data that is far superior to single "snapshot" ECG recordings, which reflect ECG activity only for the ten seconds during which the tracing is recorded. This program of research began with review of existing studies of ECG abnormalities in SAH, followed by a pilot analysis and comparative study. Based on these results, studies of prevalence, then timing and duration of ECG abnormalities were designed and implemented.

Chapter One describes the range of reported ECG abnormalities associated with SAH, as reported in the published literature, and reviews implications for patients' management and prognosis. An overview is presented of research findings on the prevalence, timing, duration, and clinical significance of these ECG abnormalities, factors believed to be associated with the changes, and theories about etiology.

In Chapter Two, a pilot analysis is described which investigated the frequency of ECG repolarization abnormalities on admission ECGs in 100 patients admitted with SAH, and the association of these ECG changes with outcome measures. This was the first investigation of ECG abnormalities in patients with SAH to utilize computerized ECG measurements, which are extremely accurate and not subject to human bias.

Chapter Three details a study which compared the initial ECGs in patients admitted with SAH with initial ECGs recorded from a normal control group. The aim of this study, which also utilized computerized ECG measurement, was to identify differences in ECG

characteristics between the two groups and to determine which waveform and interval abnormalities occur more frequently in SAH.

The next step in this program of research is described in Chapter 4. This descriptive, correlational study utilized continuous 12-lead ECG monitoring to investigate the prevalence of selected ECG characteristics and abnormalities in patients admitted with aneurysmal SAH during their intensive care unit stay. It also examined the relationship of these ECG changes to demographics, risk factors, disease severity, and outcome measures. Included in outcome measures were serum cardiac troponin level, cardiac regional wall motion score index, a measure of left ventricular function, and mortality.

Chapter 5 describes an investigation into the timing of ECG abnormalities in the clinical course after SAH. Continuous 12-lead ECG data was used to plot a timeline and analyze frequency of occurrence of ECG changes for post-SAH days. In addition, this duration of ECG abnormalities after SAH, i.e. analysis of the amount of time such ECG changes persisted in the clinical course after SAH.

These studies were designed to lay the groundwork for future research into the effects of clinical events and interventions on the ECG in patients with SAH, and perhaps formulation of ECG criteria for prediction or prevention of adverse outcomes.

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Chapter 2: Background and Significance

Electrocardiographic Abnormalities in Patients with Subarachnoid Hemorrhage

Abstract

Subarachnoid hemorrhage is a serious neurological disorder that is frequently complicated by the occurrence of electrocardiographic abnormalities unexplained by pre-existing cardiac condition. These morphological waveform changes and arrhythmias often go unrecognized or misinterpreted, potentially placing the patient at risk for inappropriate management. Many past investigations were retrospective in nature, and relied on data that were collected in an unsystematic manner. More recent studies utilizing serial electrocardiograms and Holter recordings have provided new insight into the high incidence of electrocardiographic changes in subarachnoid hemorrhage. This article reviews past research into the incidence, duration, and clinical significance of these electrocardiographic abnormalities, along with associated factors and etiological theories. Areas for future research are identified.

Subarachnoid hemorrhage (SAH) is a catastrophic neurological event that affects 30,000 persons in the United States each year (Health and Human Services, 1992). It occurs largely during young to mid adulthood in both sexes, and approximately 30% of those affected die within two weeks of the initial event (Brown& Wiebers, 1998). Mortality rates for SAH are 30 to 45% (Johnston, Selvin, & Gress, 1998; Kotila, 1984; Longstreth, Nelson, Koepsell, & van Belle, 1993), and the median age for death due to SAH is 59 years (Johnston et al.). The most common cause of SAH is rupture of a congenital aneurysm in a blood vessel at the base of the brain. Less commonly, the source of hemorrhage may be rupture of aneurysms of traumatic or infectious origin, or arteriovenous malformation.

In addition to the classic clinical signs and symptoms of SAH, which include abrupt onset of severe headache, nuchal rigidity, nausea, vomiting, and alteration in consciousness, electrocardiographic (ECG) abnormalities are frequently reported. These abnormalities include both morphological waveform changes in the 12-lead electrocardiogram and arrhythmias. While such cardiac manifestations have been associated with a wide variety of neurological events, including cerebrovascular accident, head injury, meningitis, and tumors, the highest incidence and most pronounced changes have been reported after SAH (Burch, Meyers, & Abildskov, 1954; Hersch, 1964; Yamour, Sridharan, Rice, & Flowers, 1980).

Purpose

This article describes the range of reported ECG abnormalities associated with SAH, as reported in the published literature, and reviews implications for patients' management and prognosis. An overview is presented of research findings on the

prevalence, duration, and clinical significance of these ECG changes, factors believed to be associated with the changes, and theories about etiology. Areas for future research are suggested.

Significance of ECG Abnormalities in SAH

The phenomenon of ECG abnormalities in patients with SAH was first reported in 1947 (Byer, Ashman, & Toth), but the prevalence, characteristics, and prognostic significance of the abnormalities have still not been fully explored. The etiology remains unclear, and the association with cardiac pathological changes is uncertain. Because of all these unknown factors, health care professionals who manage patients with SAH are confronted with special challenges. Some commonly used therapeutic strategies, such as infusion of pressors and large volumes of intravenous fluids, may not be optimal in patients with cardiac abnormalities (Zaroff, Rordorf, Newell, Ogilvy, & Levinson, 1999).

Because ECG changes commonly experienced by patients with SAH can mimic coronary ischemia or infarction, or can predispose patients to serious and possibly life-threatening arrhythmias, health care professionals must be able to anticipate and recognize these changes. Several case reports published since the 1950s indicate the confounding effect that ECG abnormalities can have in the management of the patient with SAH. Beard et al. (1959) described the demise of a 37-year-old woman admitted with ST segment elevation and T wave inversion. After diagnosis of myocardial ischemia, anticoagulation therapy was instituted. Although she had never exhibited neurological signs, other than brief syncope and stupor immediately before admission, she died several days later of SAH. On autopsy, she was found to have a normal heart and ruptured intracranial aneurysm. Another report (Cropp & Manning, 1960) described

postponement of surgery on a patient with SAH because of ECG changes consistent with anterior myocardial infarction. The patient died, and again autopsy findings included ruptured aneurysm and no cardiac abnormalities.

Evidence from a number of studies indicates that patients with SAH are at high risk for malignant ventricular arrhythmias, including ventricular tachycardia, torsades de pointes, and ventricular fibrillation, particularly if the corrected QT (QTc) interval is prolonged (Brouwers et al., 1989; Carruth & Silverman, 1980; Di Pasquale et al., 1987). A decrease in cardiac output due to alterations in cardiac rate associated with SAH, such as sinus bradycardia, sinus tachycardia, or rapid atrial fibrillation, also can adversely affect patients clinical status.

The relationship of ECG abnormalities to patients' outcomes is not clearly established. In earlier studies (Brouwers et al, 1989; Cruickshank, Neil-Dwyer, & Brice, 1974) of the prognostic importance of ECG changes, sample sizes were small and the results were equivocal. In a more recent retrospective study, Zaroff et al. (1999) examined mortality due to cardiac abnormalities and all causes in 58 patients with SAH and ECG changes consistent with myocardial ischemia or infarction. The results indicated that ECG abnormalities were not a significant predictor of mortality. However, 20% of patients in the source SAH database were excluded from the study because their medical records did not include ECG findings, perhaps leading to selection bias. This study was further limited by its small sample size and inclusion of only three "snapshot" ECG recordings per subject. To date, patients' outcomes have not been studied in a prospective investigation that included a large sample size.

Although SAH mortality rates have decreased slowly during the past two decades, they remain high (Johnston et al., 1998). If ECG abnormalities have developed during hospitalization, the heart of a patient with SAH who has brain death is not accepted as a donor organ because of the possibility of cardiac abnormalities. Learning more about the nature, reversibility, and optimal clinical management of ECG changes may help to increase the availability of donor hearts from this population of patients with SAH.

Incidence of ECG Abnormalities

The reported prevalence of ECG changes in patients with SAH range from 27% to 100% (Brouwers at al., 1989; Di Pasquale et al., 1987; Kreus, Kamila, & Takala, 1969; Solenski et al., 1995; Zaroff et al., 1999). This variation may be due to differences in study design, investigators' definitions of ECG abnormalities, or the methods used to evaluate ECG changes.

Retrospective studies in which subjects are selected on the basis of having one or more ECG tracings in their medical record may produce falsely exaggerated prevalences of ECG abnormalities. Because ECGs are often not recorded routinely for all patients with diagnoses of neurological abnormalities, selection based on the availability of an ECG may result in a higher proportion of subjects who had some cardiac signs or symptoms during the hospital course.

Additionally, ECGs recorded before the SAH occurred were not included in most investigations, limiting the differentiation of pre-existing ECG abnormalities from those associated with SAH. Although some researchers may consider the comparison unnecessary because patients with SAH are members of a relatively young and generally

healthy population, ECG tracings obtained before SAH should, whenever available, be compared with ECG recordings obtained after SAH.

Timing of ECG data collection may influence conclusions about the prevalence of abnormalities. In a 12-lead ECG investigation, Brouwers et al. (1989) found that the most pronounced ECG changes were demonstrated during the first 72 hours after SAH. Di Pasquale et al. (1987) found that 90% of patients had ECG abnormalities in the first 48 hours, suggesting that studies in which surveillance is started later in the course of illness may miss significant data.

Duration of ECG Abnormalities

No investigation to date has included continuous 12-lead ECG monitoring of patients with SAH, and only a few have included examination of serial tracings. Therefore, whether the observed ECG changes are transient or permanent is unclear.

In the study by Burch et al. (1954), duration of ECG abnormalities varied among subjects, exceeding 11 days for one patient. Brouwers et al. (1989) found resolution of virtually all morphological changes and arrhythmias within 12 days. In a more recent study (Kuroiwa, Morita, Tanabe, & Ohta, 1995) of 23 patients with SAH with ST elevation, the elevation normalized within one week, but changes in the T wave persisted for months. This finding confirms the observations of an earlier investigation (Shuster, 1960), in which T wave inversion was persistent. ECG changes in patients with SAH also may partially resolve, but then recur during a second SAH (Goldfinger, 1972).

Morphological ECG changes

ECG changes associated with SAH primarily reflect repolarization abnormalities involving the ST segment, T wave, U wave and QTc interval. Because of the

combination of ST segment elevation or depression and abnormal T wave morphology, myocardial ischemia or infarction is often suspected in patients with SAH. Reported frequencies of specific morphological ECG abnormalities are summarized in Table 1.

In an early study of 29 patients after surgery for SAH, Cropp & Manning (1960), found abnormal or questionable Q waves in four patients, and T wave changes indicative of myocardial ischemia in 15. One case report (White, Parker, & Rogers, 1985) describes cancellation of surgery in a patient with SAH because of sudden onset of T wave inversion and pathologic Q waves in leads II, III, and aVF consistent with inferior myocardial infarction. Despite persistent ECG changes, no cardiac enzymes indicative of

Table 1
Frequency of Morphological Waveform Abnormalities on Twelve-Lead Electrocardiograms in Patients with Subarachnoid Hemorrhage

Investigator	N	P Wave	PR Interval	QTc Interval	ST Segment	T Wave	U Wave
Shuster (1959)	12	NR	NR	NR	5 (42)	11 (92)	NR
Cropp & Manning (1960)	29	3 (10)	NR	19 (66)	13 (45)	16 (55)	8 (28)
Hersch (1964)	20	8 (40)	NR	9 (45)	10 (50)	4 (20)	8 (40)
Melin & Fogelholm (1983)	76	5 (7)	6 (8)	8 (11)	20 (26)	16 (21)	3 (4)
Di Pasquale et al. (1987)	120	17 (28)	1 (.8)	46 (44)	44 (37)	15 (12)	19 (16)
Rudehill, et al. (1987)	406	NR	17 (4)	94 (24)	62 (15)	129 (32)	190 (44)
Brouwers et al. (1989)	61	10 (16)	19 (31)	24 (39)	31 (51)	36 (59)	27 (44)
Arruda & De Lacerda (1992)	15	NR	NR	8 (53)	5 (33)	4 (27)	1 (7)

Values are number of patients (%). N indicates sample size; NR, not reported

myocardial infarction were detectable in serial samples collected during the next 48 hours, and findings on nuclear scans of the heart were normal. Surgery was performed one week later without incident. ECG changes had resolved 5 months after hospitalization.

An abnormally prolonged QTc interval with large T waves is a common finding in patients with SAH (Arruda & De Lacerda, 1992; Byer et al., 1947; Cropp & Manning, 1960; Cruickshank, Neil-Dwyer, & Brice, 1974; Hersch, 1964; Rudehill, Olsson, Sundqvist, & Gordon, 1987). Burch et al. (1954) described "some of the widest and largest T waves seen in clinical electrocardiography" in his investigation (p 720). The pattern of broad, slurred, inverted T waves associated with long QTc intervals is commonly termed "cerebral," "neurogenic," or "giant" T wave (Figure 2). Other researchers have found flattening and notching of the T wave.

Although widely reported, the prolonged length of the QTc interval was disputed by Shuster (1960). He cautioned against inadvertently including the U wave in the QTc interval. The U wave, often 1mm or greater in amplitude in patients with SAH, can be mistakenly interpreted as part of a notched T wave if the U wave occurs early during repolarization. De Sweit (1969) reported an unusual U wave abnormality in a patient with SAH. The ECG obtained one day after admission had deeply inverted U waves and elevated ST segments in the precordium. These changes were partially resolved on an ECG obtained five days later.

Although most early reports of ECG changes in SAH are case reports or studies of fewer than 60 patients, a few larger studies confirmed earlier findings. Melin and Fogelholm (1983) found ECG changes in 86% of 14 subjects who died within seven days

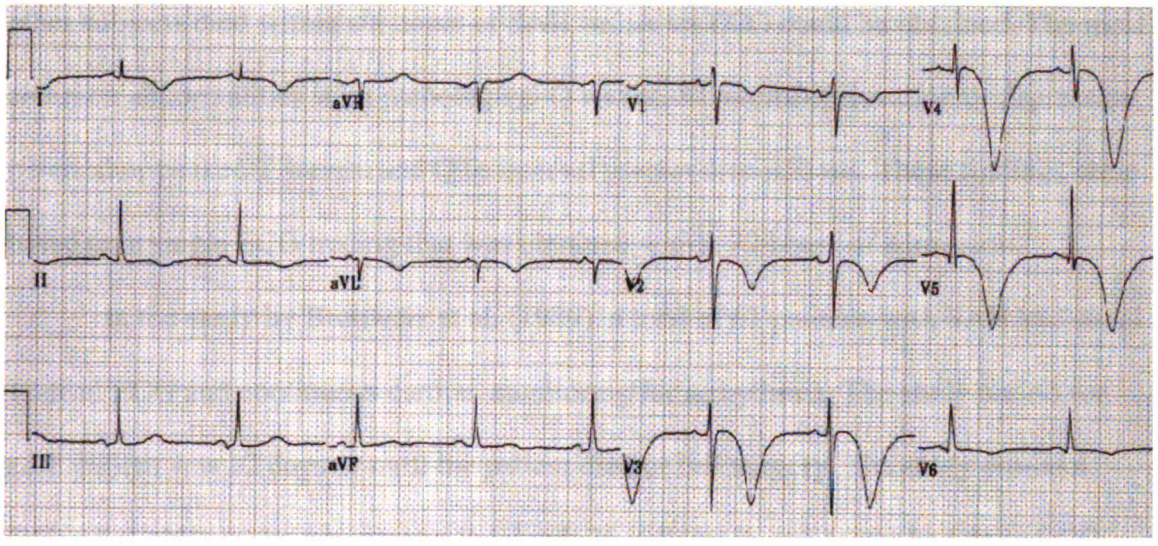

Figure 2. Twelve-lead electrocardiogram showing broad, deeply inverted "cerebral" T waves and prolonged QTc interval in a woman with subarachnoid hemorrhage.

of SAH, and in 73% of 62 subjects who survived more than seven days. A total of 26 other subjects died within six hours of SAH before an ECG could be obtained. The most common abnormalities were pathological Q waves, ST segment elevation or depression, inverted or peaked T waves, and QTc interval greater than 430 ms. These findings were based on a single ECG tracing that was obtained within 72 hours of admission.

In the study by Brouwers et al. (1989), a total of 61 patients with SAH had serial 12-lead ECG and continuous cardiac monitoring for arrhythmia. The study period for each patient was 12 days or until the patient died or had surgery. The study protocol differed slightly in the two centers involved: 26 patients in one center had daily ECG, whereas 43 patients in the other institution had ECG three times per week. Predominant morphological changes included ST segment abnormalities, prominent U wave, "ischemic" T wave, prolongation of the QTc interval, indications of left ventricular hypertrophy, flat or isoelectric T waves, and short PR intervals.

In the largest study (Rudehill, et al., 1987) to date, a single preoperative 12-lead ECG from each of 406 patients with SAH was examined. ECG findings included high amplitude R waves in 19% of subjects, ST depression in 15%, T wave abnormalities in 32%, U waves greater than 1mm amplitude in 47%, and prolonged QTc interval (>440ms) in 23%.

During a four year period, Di Pasquale et al. (1987) prospectively studied 120 patients with SAH. A 12-lead ECG was recorded at the time of admission, and 24-hour Holter monitoring was started on the same day for detection of arrhythmias. Major morphological changes detected in the 12-lead ECG tracing included ST segment changes in 37% of patients, prominent U waves in 16%, and T wave abnormalities in

12%. In addition, 42% of patients had prolonged QTc interval. Transitory ST segment depression greater than 1.5mm lasting 10 to 30 minutes was detected via the Holter recording in seven patients. ST segment elevation lasting 20 minutes occurred in one patient during cerebral angiography and concurrent with bigeminal premature ventricular complexes.

Abnormalities involving atrial depolarization, particularly peaked P waves (>2.5mm amplitude) and short PR intervals (<100ms), have also been reported (Brouwers et al., 1989; Cropp & Manning, 1960; Cruickshank, Neil-Dwyer, & Brice, 1974; de Sweit, 1972; Hersch, 1964; Syverud, 1991).

Arrhythmias

Numerous studies of cardiac arrhythmias in patients with SAH have been conducted. Reported frequencies of specific arrhythmias associated with SAH are summarized in Table 2. In earlier studies, arrhythmias were detected by using occasional 12-lead ECG and whatever cardiac monitoring apparatus was used in the clinical setting. Consequently, early reports of the prevalence of arrhythmias most likely were underestimations. Despite this flaw, similar types of arrhythmias, which generally included sinus bradycardia and sinus tachycardia, wandering atrial pacemaker, and atrial fibrillation have been detected in several studies (Cropp & Manning, 1960; Cruickshank, Neil-Dwyer, & Stott, 1974; Eisalo, Peräsalo, & Halonen, 1972; Shuster, 1960). Premature atrial, junctional, and ventricular complexes, ventricular tachycardia, and atrioventricular block have also been detected occasionally (Estañol, et al., 1979).

Several case reports describe episodes of life-threatening arrhythmias, such as ventricular tachycardia and torsades de pointes. Carruth and Silverman (1980) reported a

Table 2
Frequency of Cardiac Arrhythmias in Patients with Subarachnoid Hemorrhage

Investigator	N	ST	SB	PSVC	SVT	AF	PVC	VT
Eisalo et al. (1972)	20	5 (25)	7 (35)	NR	NR	2 (10)	2 (10)	NR
Cruickshank et al. (1974)	40	13 (33)	9 (23)	NR	NR	NR	5 (13)	NR
Estañol et al. (1979)	15	10 (67)	2 (13)	NR	NR	NR	NR	3 (20)
Melin & Fogelholm (1983)	76	7 (9)	21 (28)	NR	NR	7 (9)	8 (11)	NR
Andreoli et al. (1987)	70	NR	7 (10)	NR	5 (7)	NR	3 (4)	7 (10)
DiPasquale et al. (1987)	120	32 (27)	42 (35)	29 (24)	7 (6)	2 (2)	49 (41)	4 (3)*
Rudehill et al. (1987)	406	9 (2)	20 (5)	12 (3)†	NR	NR	12 (3)†	NR
Stober et al. (1988)	52	44 (85)	12 (23)	17 (33)	NR	2 (4)	Unifocal 17 (33) Multifocal 28 (54)	16 (29)
Brouwers et al. (1989)	61	12 (20)	31 (51)	9 (15)	4 (7)‡	4 (7)‡	9 (15)§	9 (15)§
Arruda et al. (1992)	15	4 (27)	2 (13)	0	NR	0	NR	NR

Values are numbers of patients (%)
AF indicates atrial fibrillation; N, sample size; NR, not reported; PSVC, premature supraventricular complexes; PVC, premature ventricular complexes; SB, sinus bradycardia; ST, sinus tachycardia; SVT, supraventricular tachycardia; VT, ventricular tachycardia.
* Combined non-sustained and sustained VT, ventricular flutter, ventricular fibrillation, and torsades de pointes.
† Combined PSVCs, premature nodal complexes, and PVCs.
‡ Combined supraventricular arrhythmias: atrial flutter, AF, and SVT.
§ Combined ventricular arrhythmias: PVCs, VT, ventricular flutter, and ventricular fibrillation.

dramatic case in which several runs of non-sustained ventricular tachycardia developed in a patient with SAH shortly after admission. Subsequently, the patient had a prolonged period of torsades de pointes, which also terminated spontaneously. On an ECG obtained afterward, the QTc interval was 750ms. After several days of treatment with intravenous

propranolol, ventricular arrhythmia did not recur, and the QTc interval returned to 450ms.

More recently, 24-hour 2-channel Holter monitoring has been used to detect arrhythmias in patients with cerebrovascular accident and SAH (Andreoli et al., 1989; Mikolich, Jacobs, & Fletcher, 1981; Sen et al., 1984; Stober, Anstatt, Sen, Schimrigk, & Jager, 1988). In the largest study to date in which Holter technology was used, DiPasquale et al. ((1987) first obtained a 12-lead ECG at the time of admission from a sample of 120 patients with SAH. Holter monitoring was started on the same day, and a total of 107 adequate Holter recordings were obtained. Cardiac arrhythmias were detected in 96 (90%) of the 107 patients. Premature ventricular complexes, including multiform premature ventricular complexes, couplets or triplets, and R-on-T phenomenon, were found in 49 patients (46%). Five of the patients with frequent premature ventricular complexes also had nonsustained ventricular tachycardia (defined as three or more consecutive premature ventricular complexes). Torsades de pointes occurred in four patients and progressed to ventricular fibrillation and asystole in one of the four. Holter monitoring was repeated in 48 hours for all patients with malignant ventricular arrhythmias, but no further similar arrhythmias were recorded.

Of the 107 patients, 39 (36%) had supraventricular arrhythmias, including premature supraventricular complexes and nonsustained supraventricular tachycardia, and atrial fibrillation. Thirty-two patients (30%) had sinus tachycardia (heart rate >120/min), 32 (30%) had sinus arrhythmia, 42 (39%) had sinus bradycardia (heart rate <50/min), and 23 (22%) had sinoatrial blocks. Several instances of wandering pacemaker,

sinus arrest greater than 3seconds, 2:1 atrioventricular block, atrioventricular dissociation, and idioventricular rhythm were recorded.

In correlating arrhythmias with time elapsed since SAH, Di Pasquale et al. (1987) found that both frequency and severity of arrhythmias were higher in the 62 subjects studied within 48 hours of SAH. In these patients, they found no significant difference in the duration of the QTc interval between those with and those without ventricular tachyarrhythmias. However, all patients with malignant ventricular arrhythmias had a much longer QTc interval (590$\pm$52ms) and serum levels of potassium less than 3.5 mmol/liter. Interestingly, the investigators found no correlation between clinical condition, site of aneurysm, extent of intracranial hemorrhage, age, or preexisting heart disease and the frequency and severity of arrhythmias.

This study is the most significant to date in documenting arrhythmias in patients with SAH. Because continuous 24-hour monitoring was used, the findings may be closer to the true prevalence of arrhythmia, at least for the phase of illness during which the patients were studied.

Etiological Theories

Theories about the underlying causes of ECG abnormalities in SAH are controversial, and intense investigation is ongoing. Originally, the etiology was believed to be preexisting coronary artery disease exacerbated by the physiological demands of critical illness. However, only hypertension and smoking as risk factors in both SAH and coronary artery disease, and many patients with SAH are premenopausal women with no history of coronary artery disease. Chest pain, a frequent symptom in coronary artery disease, has not been reported in association with ECG abnormalities that occur in

patients with SAH. Additionally, both coronary angiography and autopsy have revealed normal coronary vasculature in patients with SAH who had marked ECG changes (Kuroiwa et al., 1995). Cardiac injury due to elevated myocardial wall stress associated with tachycardia and hypertension has also been suggested as a causative factor. Yuki et al. (1991) proposed that coronary vasospasm and reversible post-ischemic "stunned myocardium" may influence the development of ECG changes in patients with SAH.

Increasingly, however, evidence indicates a neurogenic etiology for ECG abnormalities in SAH. Animal studies suggest interesting links between brain structures and the heart. Rogers, Abildskov, & Preston (1973) produced increases and decreases in the amplitude of the T wave by stimulating the right and left sides of the hypothalamus and stellate ganglia, respectively. These authors suggested that the mechanism is unilateral alteration of sympathetic tone to the heart. Studies in animals and humans have indicated that injury to the insula, an area of the cortex thought to be involved in arrhythmogenesis, might be implicated in both abnormal cardiac rhythm and the focal myocardial lesions sometimes seen after SAH (Oppenheimer, Cechetto, & Hachinski, 1990; Švigelj, Grad, Tekavčič, & Kiauta, 1994).

Currently, much research focuses on the release of catecholamines, either systemically or within the myocardium, as a cause of ECG abnormalities. Autopsies have revealed areas of characteristic subendocardial myocardial lesions, called contraction band necroses, in the hearts of patients dying after SAH (Brouwers et al., 1989; Doshi & Neil-Dwyer, 1977; Greenhoot & Reichenbach, 1969). The myocardial damage resembles lesions produced in animal experiments by infusion of norepinephrine (Elrifai, Bailes, Shih, Dianzumba, & Brillman, 1996). The characteristic pattern of myocardial lesions

suggested to some researchers that the damaging catecholamines are released from intramyocardial nerve endings rather than from the general circulation (Baroldi, 1992). This possibility was reinforced by investigators (Brouwers, Westenberg, & Van Gijn, 1995; Švigelj, Grad, & Kiauta, 1996) who did not find a significant relationship between plasma levels of norepinephrine and the occurrence of ECG abnormalities in patients with SAH.

Additional evidence of pathological changes in cardiac structure includes the elevated serum cardiac enzyme levels and left ventricular dysfunction that occur in some patients with SAH. Investigations (Hunt, McRae, & Zapf, 1969; Fabinyi, Hunt, & McKinley, 1977) of the relationship between levels of creatine kinase-MB and the occurrence of ECG abnormalities associated with SAH yielded conflicting results. More recently, studies focused on cardiac troponin I, a highly sensitive and specific biomarker of myocardial damage. Parekh et al. (2000) found that patients with elevations of cardiac troponin I were more likely than patients without elevations to have ECG abnormalities.

Echocardiograms have shown transient abnormalities in left ventricular wall motion in patients with SAH (Kuroiwa et al., 1995). The link between left ventricular dysfunction and ECG abnormalities in patients with SAH, however, remains unclear. Kono et al. (1994) compared two groups of patients with SAH, one group with and one group without ST segment elevation. Left ventricular wall motion was significantly decreased in the group with ST segment compared with the group without ST elevation. In another study (Mayer et al., 1995), five subjects from a total sample of 57 patients with SAH had abnormalities in left ventricular wall motion, and a significant association was observed between abnormal findings and symmetrically inverted T waves. Conversely, in

a study of 45 patients with SAH, Davies et al. (1991) found that ECG was not an accurate predictor of myocardial function in four subjects with SAH who had abnormal findings on echocardiograms. All such investigations to date, however, have been limited by small sample sizes, and studies with larger sample sizes are needed to clarify the relationship between left ventricular dysfunction and ECG abnormalities. Samuels (1987) has theorized that neurogenic influence over cardiac function might exist as a continuum, with mild, reversible ECG changes at one end of the continuum and severe, irreversible myocardial degeneration at the other end.

The relationship between the occurrence of ECG abnormalities and neurogenic pulmonary edema in patients with SAH has not been determined. Although the pathogenesis of neurogenic pulmonary edema is not completely understood, most researchers believe that the abnormality is noncardiogenic, resulting primarily from injury to the pulmonary circulation. However, in a study of patients with SAH and subsequent neurogenic pulmonary edema, Mayer et al. (1994) found evidence that neurogenic left ventricular dysfunction, in combination with noncardiogenic mechanisms, may contribute to formation of pulmonary edema. Further investigation is needed to clarify the pathogenesis of pulmonary edema in patients with SAH, and to determine if the edema is associated with ECG abnormalities.

Factors that may influence the development of arrhythmias in patients with SAH include cerebral vasospasm, hypoxia, electrolyte imbalance, and sudden increase in intracranial pressure triggering a sympathetic or vagal discharge from compression of brain structures. Injection of blood into the subarachnoid space of rats can produce sinus bradycardia and tachycardia, and a large number of other arrhythmias (Lorenzo, Earle,

Peterson, Todd, & Leibrock, 1994). This finding suggests that the basic hemorrhagic nature of SAH may play a role in producing arrhythmias in the period immediately after hemorrhage.

Limitations of Existing Studies

The first report of ECG abnormalities in patients with neurological problems was published more than 50 years ago. Research began largely with case reports describing the phenomenon, followed by studies with small sample sizes comparing the prevalence of ECG changes in various neurological conditions such as cerebral vascular accident, trauma, meningitis, and intracranial tumors. It soon became apparent that ECG abnormalities were more frequent and pronounced in patients with SAH than in patients with other neurological disorders.

Studies specifically concerned with ECG changes in SAH have examined, prevalence, characteristics, and associated factors, but many questions remain. Many of the earlier studies were retrospective reviews of medical records. This method presents a potential weakness, because most likely ECGs were not obtained routinely and may have been reserved for those who were clinical unstable. Another weakness in virtually all previous research is a lack of systematic collection of ECG data on either a continuous or a consistent basis.

Rudehill et al. (1987) collected ECG data on a very large sample (n=406) of patients with SAH. However, ECGs were limited to a single preoperative tracing for each patient, and were not obtained at any particular time after diagnosis of SAH. Unlike the situation in most previous studies, a well-documented and widely accepted classification system was used to evaluate ECG abnormalities. Although this investigation yielded a

great deal of data, the episodic nature of the ECG recordings somewhat limits its usefulness.

Brouwers et al.(1989) were among the first to collect data prospectively in a relatively systematic manner. However, the ECG data were limited to a single tracing for each 24 hours in the study for some patients and to only one tracing in 72 hours for the remainder of patients. Most likely, ECG changes were missed because of the snapshot nature of the recordings.

Perhaps the most complete and informative investigation to date was that of Di Pasquale et al (1987). Data from their one-time 24-hour Holter recording were striking. These authors reported some of the highest prevalences of arrhythmias, most likely because of the continuous nature of the monitoring. ST segment changes and transient arrhythmias of every type were recorded in the 107 patients who had Holter monitoring. Of particular interest were the four cases of torsades de pointes. Although the results are limited because the patients had Holter monitoring only once, this study provides some of the best information thus far on cardiac arrhythmias in patients with SAH. The findings also confirm that methods used in the past were inadequate to detect the true scope of arrhythmias in patients with SAH. This study was also limited because the continuous Holter monitoring reflected only two ECG leads and thus possibly missed QT or ST changes that occurred in unrecorded leads.

Directions for Future Research

Much remains to be learned about the phenomenon of ECG abnormalities in patients with SAH. Unanswered questions include those about prevalence, contributing

factors, etiology, and prognostic significance. Some specific areas for future research are listed in Table 3.

Carefully designed, prospective studies with large sample size are needed to effectively address these questions. Continuous, systematic multi-lead - preferably 12-lead - acquisition of ECG data is necessary to establish the prevalence, duration, and timing of ECG abnormalities in the clinical course of SAH. Precise, well-accepted definitions and accurate measurement of ECG amplitudes and intervals are essential elements of any study of ECG abnormalities.

Table 3
Areas for future research in patients with subarachnoid hemorrhage

What morphological ECG abnormalities are common in patients with SAH?
What cardiac arrhythmias occur in patients with SAH?
What is the frequency and duration of ECG abnormalities, and at what phase of the clinical course do they occur?
Do ECG abnormalities associated with SAH resolve over time, or are they permanent?
What clinical variables are associated with these ECG abnormalities? Variables may include increased intracranial pressure, cerebral vasospasm, and measures of neurological status such as Glasgow Coma Scale score (Teasdale & Jennett, 1974) and Hunt-Hess SAH grade (Hunt & Hess, 1969).
What demographic variables are associated with the phenomenon? Variables includes age, sex, ethnic group, and coronary risk factors.
What are the effects of common nursing and medical interventions on ECG abnormalities? Interventions may include neurosurgery, neurovascular interventional procedures, cerebral angiography, "HHH" therapy (hypervolemia, hypertension, hemodilution), calcium channel blocker therapy for vasospasm prevention (nimodipine).
What is the association between these ECG abnormalities and indices of abnormal myocardial function, such as detection of abnormal serum levels of cardiac enzymes or ventricular wall motion abnormalities?
Are any of these ECG abnormalities predictive of in-hospital mortality?
Do any of these ECG abnormalities disqualify the use of an SAH patient's heart for cardiac transplantation?

Summary

SAH is a serious neurological disorder that is often complicated by the occurrence of ECG abnormalities unexplained by pre-existing cardiac conditions. In particular, ECG changes that occur during cardiac repolarization, such as abnormalities in the ST segment and the T wave, must be interpreted in the context of the patient's neurological abnormalities. Neurologically mediated ECG changes are often misdiagnosed as myocardial ischemia or infarction, resulting in delayed treatment of the primary problem. Routine measurement of the length of the QTc interval in patients with SAH may help detect predisposition to potentially lethal tachyarrhythmias, particularly if the patient also has low serum levels of potassium.

Investigation into the frequency, characteristics, and prognostic significance of ECG abnormalities in patients with SAH will provide essential information about the underlying neurological, biochemical, or cardiac processes. Systematic ECG monitoring for both morphological changes and arrhythmias could add significantly to what is known about the nature of these ECG changes and their clinical implications. Previous research on ECG abnormalities in the setting of SAH has just touched the surface, and a great deal needs to be learned for optimal management of patients with SAH.

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Chapter 3: Pilot Analysis

Electrocardiographic Repolarization Abnormalities in Subarachnoid Hemorrhage

Abstract

Electrocardiographic abnormalities, particularly in those waveforms representing ventricular repolarization, have been reported in subarachnoid hemorrhage (SAH). This study reports abnormalities on the initial electrocardiogram in 100 patients with SAH. Overall, one or more repolarization abnormalities occurred in 41% of patients. Analysis revealed prolonged QTc interval >460ms in 16%, ST segment elevation in 9%, ST depression in 3%, T wave inversion in 7%, and U wave ≥100μV in 15%. Electrocardiographic criteria for left ventricular hypertrophy were met in 14%, and 43% of those patients had no history of hypertension. Serum cardiac troponin I was elevated in 21%, and was significantly associated with QTc interval >460ms ($p<.001$). Controlling for gender, those with QTc interval >460ms were 5.5 times more likely to have elevated serum cardiac troponin I. It is concluded that repolarization abnormalities are present in a high proportion of patients with SAH. Some SAH patients also have left ventricular hypertrophy voltage unrelated to hypertension or coronary artery disease. Prolonged QTc interval after SAH is significantly related to myocardial injury, but unrelated to mortality, and there is no association between ST-T wave abnormalities and either myocardial injury or mortality.

Subarachnoid hemorrhage (SAH) is a catastrophic neurological event that affects 30,000 persons annually in the United States (Health and Human Services, 1992). It is caused most commonly by rupture of an aneurysm in a cerebral artery at the base of the brain, resulting in damage to brain structures. In addition to neurological signs and symptoms, including severe headache with abrupt onset, nausea, vomiting, nuchal rigidity, and decreased level of consciousness, electrocardiographic (ECG) abnormalities unexplained by pre-existing coronary artery disease (CAD) are frequently are reported. These abnormalities are often unrecognized or misinterpreted, potentially placing the patient at risk for inappropriate management. In addition, the hearts of patients dying from SAH may be rejected for transplant because of the occurrence of ECG abnormalities that are strikingly similar to those usually associated with CAD.

This study investigates the frequency of ECG repolarization abnormalities on the initial ECG in patients admitted with SAH, and the association of these ECG changes with outcome measures.

Materials and Methods

Sample and Setting

As part of an ongoing prospective study of cardiac responses to SAH, continuous 12-lead ECG monitoring was conducted during hospitalization in the neurological intensive care unit. The parent study, Cardiac Response to Aneurysmal Subarachnoid Hemorrhage (CRASH), included all consenting adult patients admitted with aneurysmal subarachnoid hemorrhage to the NICU of a major academic medical center. Patients with subarachnoid hemorrhage of traumatic or infectious origin, or due to arteriovenous malformation, were not included in the study. This pilot analysis includes data from the initial 12-lead ECG

recorded at the beginning of this period of continuous 12-lead ECG monitoring for the first 100 patients enrolled in the parent study.

Instruments and Procedure

The 12-lead ECG was recorded as soon as possible after patient enrollment, utilizing the Mortara ELI 100 ST Monitor (Milwaukee, WI). The Mortara ST monitor is a portable, programmable, microprocessor-based device, which samples electrical potentials from all 12 leads at 4ms intervals over a 10-second period to identify a noise-free median beat. From this median beat, the device measures ST segment deviation relative to the PR segment to a minimum resolution of 10μV.

Electrocardiograms stored in the ST monitor were downloaded to the Mortara ST Review Station, a personal computer with additional ST segment analysis software. This software provides quantitative ST segment measurements in microvolts for each of the 12 leads, as well as QTc interval duration in milliseconds. Analysis of other ECG waveforms and intervals, including T wave amplitude and QRS amplitude, was accomplished utilizing Questicus software (Inovise Medical, Inc., Newberg, OR), which presents data recorded by the Mortara ST monitor as quantitative waveform measurements in tabular form. Because computerized measurement was not available for U wave amplitude, it was assessed visually. Standard ECG criteria for LVH were applied to all ECGs.

Definitions

A QTc interval >460ms was considered prolonged. A U wave with amplitude ≥100μV was defined as abnormal. Criteria recommended jointly by the European Society of Cardiology and American College of Cardiology for myocardial ischemia were used to

define ST segment elevation and depression and T wave inversion (Myocardial infarction redefined, 2000). Using these definitions, the ST segment is considered elevated when it is ≥200μV above the PR segment baseline in leads V_1-V_3, or ≥100μV above the PR segment baseline in other leads, in two contiguous leads when measured at the J point. ST segment depression is present when the ST segment is ≥100μV below the PR segment baseline in two contiguous leads when measured at the J point. T wave inversion occurs when there is a T wave with negative deflection ≥100μV in two contiguous leads.

Cardiac troponin I (cTnI) was considered elevated when it was >1.0μg/L, which is accepted as indicative of substantial myocardial necrosis at the study medical center.

Statistical Analysis

Descriptive statistics (frequencies and proportions) were used to report the number and type of ECG abnormalities. Chi-square analysis was used to test relationships between ECG parameters and patient characteristics. Logistic regression was used to investigate which ECG abnormalities may be predictive of elevated cTnI. A *p* value <.05 was considered to be statistically significant.

Results

Sample Characteristics

The sample included 100 patients admitted with a diagnosis of aneurysmal SAH. The sample demographics included a mean age of 53 years (±36), 66% women, and 34% men. Ethnicity included white, 63%; Asian, 12%; black, 10%; Latino, 14%; and unknown, 1%. Mean Hunt-Hess SAH grade was 2.34. This is a measure of neurological status on admission in SAH patients, and possible grades range from 1, designating minimal or no symptoms, to 5 designating coma.

Forty-three percent of patients had a past medical history of hypertension, and 52% had a history of cigarette smoking. There was no history of coronary artery disease in 95% of enrolled patients.

Frequency of ECG Abnormalities

The baseline cardiac rhythm was normal sinus rhythm in 93%. Baseline rhythm in the remaining seven patients included sinus tachycardia in four, sinus bradycardia in one, and atrial fibrillation in two.

Prolonged QTc interval was found in 16% of patients (Figure 3), and all of these were female. No patients had ST segment elevation when amplitude was measured at the J point, but 9% had ST segment elevation when it was measured at J+60ms (Figure 4). Three percent of patients had ST segment depression, 7% had T wave inversion, and 15% had abnormal U wave (Figure 5). One or more repolarization abnormalities (QTc interval prolongation, ST segment deviation, T wave inversion, or abnormal U wave) were found in 41% of patients, and these occurred significantly more frequently in those with a history of hypertension ($p=.027$) or smoking ($p=.030$).

Standard ECG criteria for LVH were met in 14% of patients. Of this 14%, none had a history of CAD, and 43% had no history of hypertension.

Serum cardiac troponin I (cTnI) was elevated in 21% of patients, and an elevated cTnI was significantly associated with prolonged QTc interval ($p<.001$), but not with ST segment deviation, T wave inversion, or abnormal U wave. Controlling for gender, those with prolonged QTc were still 5.5 times more likely to have elevated cTnI. Sixteen percent of the patients in this study died during hospitalization, but no significant association was found between mortality and any single or aggregate ECG parameters.

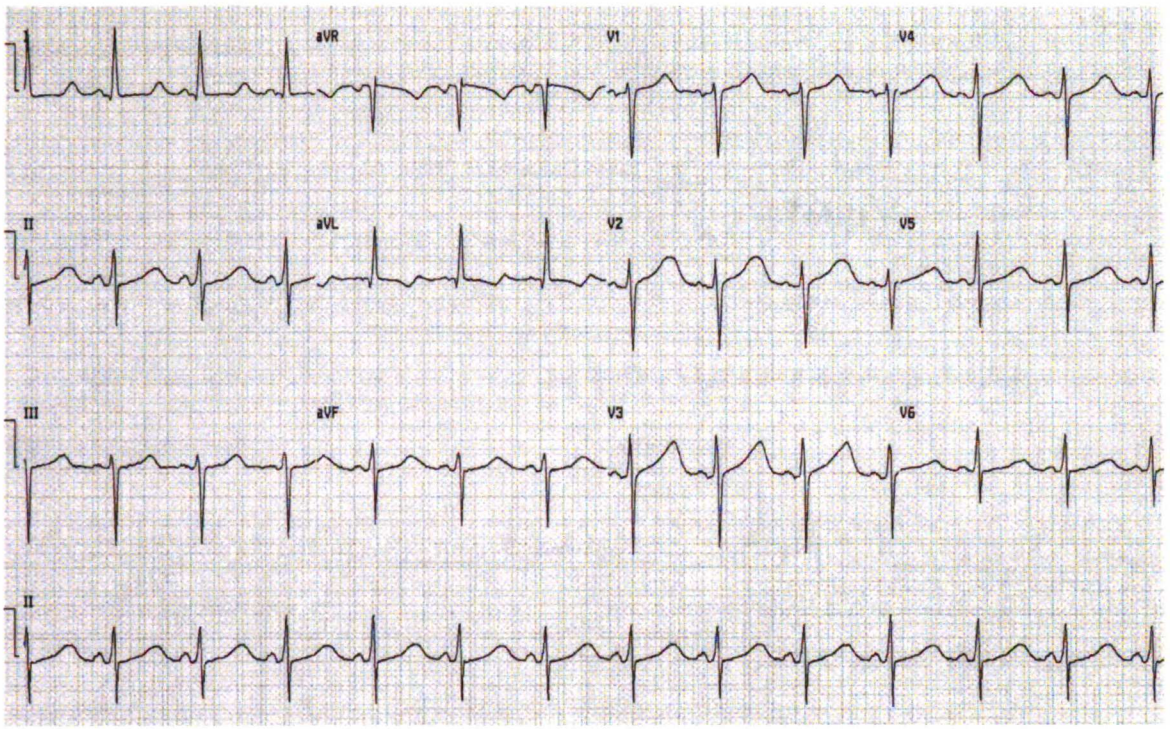

Figure 3. Prolonged QT interval (581ms) in a patient with subarachnoid hemorrhage.

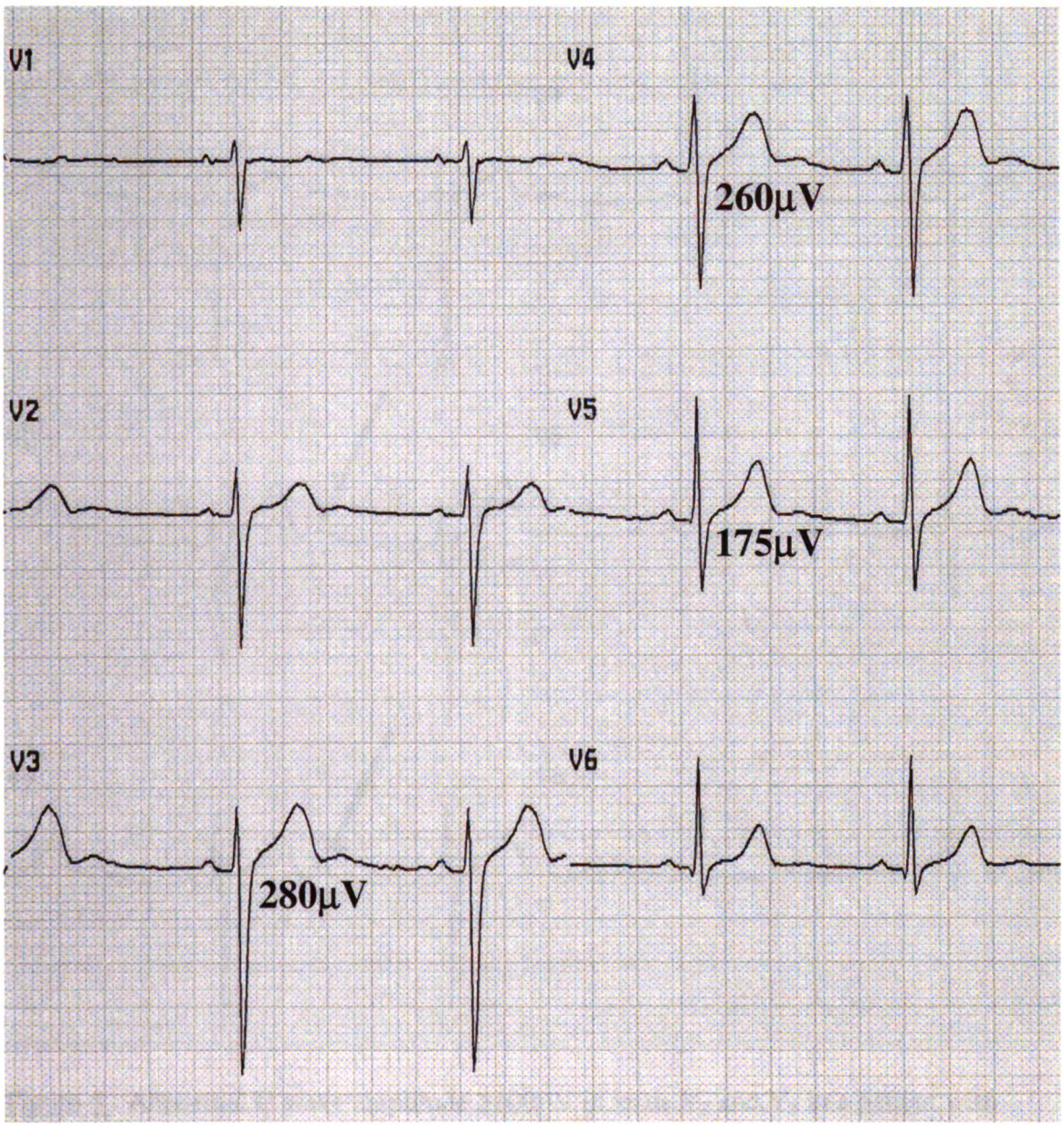

Figure 4. ST elevation at J+60ms in leads V_3, V_4, and V_5 in a patient with subarachnoid hemorrhage.

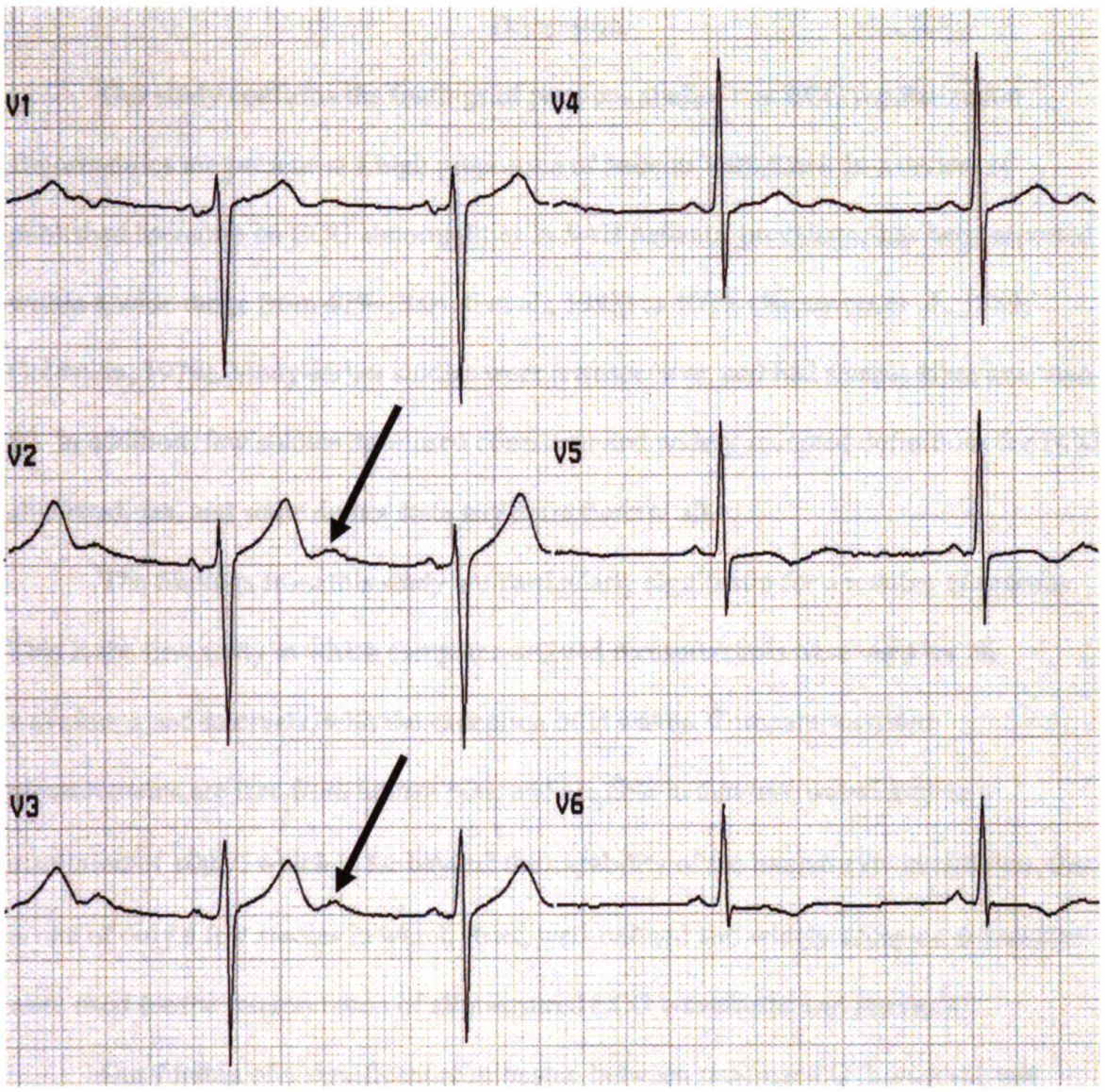

Figure 5. Abnormal U wave amplitude ≥100μV in leads V_2 and V_3 in a patient with subarachnoid hemorrhage.

Discussion

Our study confirms the findings of previous studies that ECG repolarization abnormalities are present in a high proportion of patients with SAH. In a review of published literature on ECG abnormalities in SAH patients, prevalence has been reported within a wide range from 47% (Salvati et al., 1992) to 100% (Brouwers et al., 1989; Goldstein, 1979). Many earlier studies were retrospective, and had sample sizes less than 50. In addition, few studies have used consistent and widely accepted definitions for ECG abnormalities, and some do not state any definitions at all.

The findings from this study are particularly significant for a number of reasons. This is the first study in which computer-assisted measurements were used for all waveforms and intervals, with the exception of U waves. Computer-assisted measurements are free from human bias, and are able to measure waveforms to a resolution of 10μV, which is far beyond the capability of the human eye. In addition, this is one of only a few studies in which strict, well-defined and widely accepted definitions were used for the interpretation of all measured ECG waveforms and intervals.

Our finding of a significant relationship between prolonged QTc interval and elevated cTnI, a biomarker of myocardial cell death, has not been reported previously. Although the precise mechanism of QTc interval prolongation after SAH is unknown, one widely held theory that would explain the ECG abnormalities observed in this study is that of excessive release of norepinephrine from the sympathetic nerve terminals in the heart, which results in patchy subendocardial myocardial necrosis (Greenhoot & Reichenbach, 1969). Such injury may cause an elevated serum troponin and prolong repolarization as the wavefront progression is hindered by scattered areas of necrosis

(Drislane, Samuels, Kozakewich, Schoen, & Strunk, 1987; Parekh et al., 2000). Excessive sympathetic outflow after SAH has also been hypothesized to be a major causative factor of other cardiac responses including myocardial wall motion abnormalities (Zaroff, Rordorf, Ogilvy, & Picard, 2000), and neurogenic pulmonary edema (Mayer et al., 1994).

In this study, we also found cases of LVH voltage unrelated to hypertension or known CAD. Increased prevalence of LVH voltage in SAH patients has been reported previously, but its association with hypertension or CAD has not been reported. The origin of this finding after SAH has not been completely explored, and in the past has been explained by history of hypertension, which is a known risk factor for SAH. An alternative explanation for increased QRS voltage is that of increased intracardiac blood volume (Brody, 1956) due to "triple H" therapy (hypervolemia/ hemodilution/ hypertension), commonly used to prevent or treat cerebral vasospasm after SAH. However, this theory is weakened by the fact that increased QRS amplitude was reported in the literature decades before the advent of this form of vasospasm management.

Limitations of the Study

Only one 12-lead ECG was collected on each patient in this analysis. This limits the data to only a "snapshot" view of the patient's ECG status, and precludes analysis of any transient or dynamic ECG abnormalities. An ongoing study utilizing continuous 12-lead ECG recording will provide not only more complete information on the prevalence of ECG changes, but also on the duration of such abnormalities and their timing in the clinical course.

As with most ECG studies of patients with neurological diagnoses, this study was

limited by absence of an ECG recorded prior to the SAH event to differentiate pre-existing abnormalities from those truly associated with SAH. Because patients presenting with SAH are relatively young and in good general health, they may never have had an ECG recorded.

Conclusions

Repolarization abnormalities are present in a high proportion of patients with SAH. These patients also have LVH voltage unrelated to hypertension or coronary artery disease. Prolonged QTc after SAH is significantly related to myocardial injury, but was not demonstrated to be related to mortality, and there is no association between ST-T wave abnormalities and either myocardial injury or mortality. An ongoing continuous 12-lead ECG study will determine whether ECG changes resolve over time.

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Chapter 4: Electrocardiographic Abnormalities in Patients with Subarachnoid Hemorrhage and Normal Adults: A Comparison Study

Subarachnoid hemorrhage (SAH) is a serious neurological condition affecting 30,000 persons annually in the United States (Health and Human Services, 1992). It is most commonly a result of rupture of an aneurysm in a cerebral artery at the base of the brain, frequently with devastating results. The mortality rate from SAH has been reported from 30% to 67% (Bamford, Sandercock, Dennis, Burn, & Warlow, 1990; Bonita & Thomson, 1985; Kotila, 1984; Longstreth, Nelson, Koepsell, & van Belle, 1993), and more than 30% of surviving patients are left with some degree of neurologic deficit (Ingall, Whisnant, Wiebers, & O'Fallon, 1989). Electrocardiographic (ECG) abnormalities are frequently reported in patients with SAH, generally in the absence of history of cardiac disease. Because these ECG abnormalities bear a striking resemblance to those associated with myocardial ischemia or infarction, they may be misinterpreted as a primarily cardiac disorder. Initiation of diagnostic or interventional procedures or surgery indicated for definitive management of SAH may be delayed as a result of this misinterpretation. In addition, hearts of patients dying from SAH may be rejected for transplant because the occurrence of ECG abnormalities may lead clinicians to believe that the patient has coronary artery disease (CAD).

Knowledge of the types of ECG abnormalities that occur in association with SAH is essential in order to understand their implications for patient management and outcomes. This study compared initial ECGs in patients admitted with SAH with initial ECGs recorded from a normal control group, to identify differences in ECG characteristics

between the two groups and to determine which waveform and interval abnormalities occur more frequently in SAH.

Materials and Methods

Sample and Setting

The SAH group was comprised of all consenting patients admitted consecutively to the neurological intensive care unit in a major university medical center. Because bundle branch block (BBB) and normal variant early repolarization can cause artifactual deviation of the ST segment and T wave, patients with SAH who were found upon initial screening to meet ECG criteria for these conditions were excluded from the SAH comparison group.

ECG data from normal adults were obtained from a prospective clinical trial involving continuous 12-lead ECG monitoring (Drew et al., 1999). This database provided the best available comparison group because data were acquired using the same ECG recorder, software, and procedures as those described for the SAH group. Analysis methods utilized for this data were identical to that used to analyze data from patients with SAH, and research assistants in both studies received the same training in data collection and management procedures.

Those included in the normal group were patients who were evaluated in the emergency department, then discharged to home. Patients were excluded if the medical record documented coronary artery disease, prior myocardial infarction or ischemia, angina or anginal equivalent, or any other cardiac diagnosis after medical evaluation. Then, the initial 12-lead ECG recordings or all remaining patients were screened for

BBB, left ventricular hypertrophy (LVH), prior myocardial infarction, and normal variant early repolarization, and the presence of any of these ECG patterns resulted in exclusion.

Instruments and Procedure

ECG data were recorded using the Mortara ELI 100 ST Monitor (Milwaukee, WI), a portable, programmable, microprocessor-based device, which samples electrical potentials from all 12 leads at 4ms intervals over a 10-second period to identify a noise-free median beat. From this median beat, the device measures and records a total of 391 different ECG intervals, amplitudes, and derived parameters. It should be noted that by convention, lead aVR is computed as –aVR by Mortara equipment, resulting in positive waveform values that may be unfamiliar to the reader. ECG data were processed in the Mortara ST Review Station computer, then converted to quantitative waveform measurements in tabular form using Questicus software (Inovise Medical Inc., Newburg, OR). The resultant table presents 391 measurements, which include 32 separate amplitude and duration measurements and several derived parameters for each of the 12 leads, as well as seven summary measurements averaged over all 12 leads. Because computerized measurement is not available for U wave amplitude, U waves were assessed visually using a manual ECG magnifying device. Definitions of ECG diagnostic criteria and abnormalities, shown in Table 4, were used in constructing dichotomous variables (present versus absent) for ECG abnormalities in this comparison study.

Statistical Methods

Some of the 391 ECG measurements in the Questicus program may, by their very nature, contain a large number of missing values, depending on the morphology of the lead being measured. For example, the program measures Q wave amplitude and duration

Table 4
ECG Operational Definitions

Variable Name	Definition
Short PR	≤120ms
Prolonged QTc	Males >450ms , females >460ms
ST elevation at J	≥200μV in V_1 or V_2 or V_3 ,*or* ≥100μV in any other lead, measured at J point
ST elevation at J + 60ms	≥200μV in V_1 or V_2 or V_3 ,*or* ≥100μV in any other lead, measured 60ms after J point
ST depression at J	≥100μV in any leads, measured at J point
ST depression at J + 60ms	>100μV in any leads, measured 60ms after J point
T wave inversion	Negatively deflected Amplitude >100μV in any lead with predominantly positive QRS complex (excluding V_1 & V_2)
U wave elevation	Separate positive wave after T wave and before next P wave Amplitude >100μV
T2 deflection	Distinct positive waveform superimposed on downslope of T wave
Bundle branch block criteria	▪ QRS duration ≥120ms (RBBB) or >120ms (LBBB), *and* ▪ Terminal broad S wave in I and rsR' or notched R in V_1 (RBBB), *or* ▪ Monophasic notched R and no Q or S in I, and dominant S or QS in V_1 & V_2 (LBBB)
LVH criteria	▪ R aVL >9mm(F), >11mm (M), *or* ▪ R aVL +S V_3 >20mm (F), >25mm (M), *or* ▪ S V_1 + R V_5 or R V_6 (whichever is taller) >35mm (age >35), *or* ▪ R V_6 > R V_5 (only if R V_5 & R V_6 >7mm) (Evans, 1997; Evans, 1999)

for all 12 leads, and missing values (i.e., absent Q wave) would be expected in a normal ECG recording. Likewise, missing values would be expected in most cases when the R' or S' amplitude is measured. For statistical reasons, only those variables that had ≤10% missing values in the normal and SAH groups were selected (≥27 values in the normal group and ≥180 values in the SAH group). This resulted in 237 variables retained for analysis of each 12-lead ECG.

Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. Normally distributed continuous variables were analyzed using the

independent samples t test, while those with non-normal distributions were analyzed with the Mann-Whitney U test.

Ten dichotomous variables identifying specific ECG abnormalities were constructed using quantitative ECG measurements. Descriptive statistics (frequencies and proportions) were used to report the number and type of ECG abnormalities. Fisher's Exact Test was used to test associations between these ECG abnormalities and group designation. A p value <.05 was considered significant throughout this study.

Results

Sample Characteristics

In the SAH group, one patient who lacked a technically acceptable ECG on admission was excluded. Eight patients with SAH were excluded because of BBB, and one patient was excluded because of early repolarization pattern, resulting in a sample size of 200.

From the control database (n= 621), 54 patients were identified who had no cardiac diagnoses and were discharged to home from the emergency department after medical evaluation. Seven or the 54 patients did not have a technically acceptable initial ECG, and were excluded from the normal group. Standard ECG screening criteria were applied to the initial 12-lead ECG recordings of the remaining 47 patients to exclude those with BBB (n=1), left ventricular hypertrophy (LVH) (n=9), prior myocardial infarction (n=3), and normal variant early repolarization (n=4). As a result of this selection procedure, 30 normal patients were identified.

Diagnoses of patients in the normal group included atypical/non-cardiac chest pain in 70% (n=21), gastric/abdominal pain in 17% (n=5), muscular pain in 10% (n=3),

Table 5
Demographic Profile of Normal and SAH Groups

	Normal Group n=200	SAH Group n=30	p value
Age	57 (12.78)	55 (13.12)	NS
Female gender	17 (57%)	136 (68%)	NS
Ethnicity:			NS
Asian/Pacific Islander	3 (10%)	32 (16%)	NS
Black, not of Hispanic origin	7 (23%)	18 (9%)	NS
Hispanic	2 (7%)	22 (11%)	NS
White, not of Hispanic origin	18 (60%)	128 (64%)	NS

Age indicates years (standard deviation)
All other values are number of patients (%),

and other non-cardiac diagnoses in 3% (n=1). Analysis of age, gender, and ethnicity data revealed no statistically significant differences between the SAH and normal groups (Table 5).

ECG Data

Analysis of continuous ECG measurements revealed significant differences between the normal and SAH groups in a number of areas, with the most striking differences in R and S wave amplitudes (Table 6). The mean R wave amplitude was 160μV greater in lead I (p=.001) and 113μV greater in lead V_2 (p=.016) in normal patients. However, the most extreme difference was in lead V_6, where the mean R wave amplitude was 308μV higher in patients with SAH (p=.003).

The mean R wave amplitude in lead –aVR, which is analogous to the S wave in the conventional lead aVR, was 129μV greater in normal patients than in SAH patients (p=..028). Mean S wave amplitude was significantly higher in SAH patients than in normal patients in all precordial leads, with differences ranging from 49μV in lead V_6 to

Table 6
Differences Between Normal Group and SAH Group Reaching Statistical Significance

Lead	Variable	Normal Group Mean	SAH Group Mean	p value (95% CI)
12-lead	PR interval	158ms	139ms	.000 ✓
12-lead	QRS duration	91ms	88ms	.018
12-lead	T wave axis	48	67	.001
I	R wave maximum amplitude	680μV	518μV	.001 ✓
I	R wave area	14581ms μV	11306ms μV	.005
I	QRS area	8541ms μV	6572ms μV	.001
I	ST amp at J point	17μV	1μV	.000
I	ST amp at J+40	23μV	4μV	.000
I	ST amp at J+60	31μV	7μV	.000
I	ST amp at J+80	38μV	12μV	.000
I	ST amp at J absolute value	21μV	12μV	.005
I	ST amp at J+40 absolute value	27μV	14μV	.002
I	ST amp at J+60 absolute value	35μV	16μV	.000
II	T wave area	32555ms μV	27952ms μV	.015
II	ST amp at J point	18μV	2μV	.008
II	ST amp at J+40*	28μV	12μV	.010 (4.06μV–29.11μV)
II	ST amp at J+60 *	38μV	21μV	.013 (3.57μV–30.40μV)
II	ST amp at J+80	49μV	31μV	.023
III	R wave duration	40ms	48ms	.043
-aVR	R wave maximum amplitude *	860μV	730μV	.028 ✓ (13.97μV–244.81μV)
-aVR	R wave area	19345mm μV	15772ms μV	.021
-aVR	QRS area	10791mm μV	9064ms μV	.015
-aVR	T wave area	28309mm μV	20244ms μV	.000
-aVR	ST amp at J point	18μV	1μV	.001
-aVR	ST amp at J+40	25μV	8μV	.001
-aVR	ST amp at J+60	34μV	14μV	.000
-aVR	ST amp at J+80	43μV	22μV	.001
-aVR	ST amp at J+60 absolute value	36μV	23μV	.001

Lead	Variable	Normal Group Mean	SAH Group Mean	p value (95% CI)	
aVL	R div Q	5.07	4.07	.036	
aVL	ST amp at J point	8μV	0	.040	
aVL	ST amp at J+40	8μV	-2μV	.007	
aVL	ST amp at J+60	12μV	-3μV	.001	
aVL	ST amp at J+80	14μV	-4μV	.001	
aVL	ST amp at J point absolute value	16μV	12μV	.032	
aVL	ST amp at J+60 absolute value	23μV	14μV	.001	
V_1	R wave duration	28 ms	24ms	.008	
V_1	S wave maximum amplitude	-702μV	-889μV	.027	✓
V_1	R div Q	133	13	.000	
V_1	QS	733	1136	.000	
V_2	R wave duration	36ms	30ms	.000	
V_2	R wave maximum amplitude	483μV	370μV	.016	✓
V_2	S wave maximum amplitude	-865μV	-1081μV	.027	✓
V_2	R div Q	483	36	.000	
V_2	QS	865	1336	.000	
V_2	R wave area	8270ms μV	5972ms μV	.009	
V_2	S wave area	20235ms μV	28116ms μV	.013	
V_2	T wave area	46776ms μV	37190ms μV	.015	
V_2	ST amp at J point	58μV	40μV	.045	
V_2	ST amp at J+40	93μV	69μV	.032	
V_2	ST amp at J+60	109μV	80μV	.017	
V_2	ST amp at J+80	130μV	96μV	.009	
V_2	ST amp at J point absolute value	60μV	44μV	.049	
V_2	ST amp at J+40 absolute value	93μV	70μV	.039	
V_2	ST amp at J+60 absolute value	109μV	81μV	.018	
V_3	R wave duration *	47ms	40ms	.004 (2.22ms-11.20ms)	
V_3	S wave maximum amplitude	-595μV	-898μV	.005	✓
V_3	R div S	43	1	.002	
V_3	QS	597	901	.005	
V_3	R wave area	18288ms μV	14810ms μV	.039	
V_3	S wave area	11759ms μV	20038ms μV	.007	

Lead	Variable	Normal Group Mean	SAH Group Mean	p value (95% CI)
V_4	S wave maximum amplitude	-277μV	-460μV	.016 ✓
V_4	R div S	67	25	.033
V_4	QS	307	523	.004
V_4	S wave area	5071ms μV	8928ms μV	.022
V_4	ST amp at J point	31μV	4μV	.001
V_4	ST amp at J+40	46μV	23μV	.010
V_4	ST amp at J+60	59μV	34μV	.011
V_4	ST amp at J+80	71μV	47μV	.050
V_4	ST amp at J+60 absolute value	61μV	46μV	.046
V_5	R wave duration	60ms	51ms	.006
V_5	S wave maximum amplitude	-107μV	-209μV	.010 ✓
V_5	R div Q	13	41	.007
V_5	ST amp at J point	18μVV	-3μV	.001
V_5	ST amp at J+40	26μV	6μV	.004
V_5	ST amp at J+60	32μV	13μV	.006
V_5	ST amp at J+80	42μV	23μV	.019
V_6	R wave duration	69ms	57ms	.000
V_6	R wave maximum amplitude	929μV	1237μV	.003 ✓
V_6	S wave maximum amplitude	-44μV	-93μV	.022 ✓
V_6	R div Q	12	20	.001
V_6	QRS complex area	12369ms μV	15028ms μV	.047
V_6	ST amp at J point	16μV	-3μV	.000
V_6	ST amp at J+40	15μV	-2μV	.002
V_6	ST amp at J+60	19μV	3μV	.004
V_6	ST amp at J+80*	26μV	9μV	.014 (3.32μV-29.20μV)

*Analyzed with independent samples t test; all others analyzed with Mann-Whitney U test.

✓ Indicates clinically significant difference (see text).

303μV in lead V_3. In another clinically significant finding, the mean R interval was 19ms shorter in the SAH group (p=000). A 19 degree T wave axis difference was also noted between the two groups (p=.001).

There were statistically significant differences between the normal and SAH groups in 91 of the ECG quantitative variables. However, some of these differences were numerically small and may not indicate clinical significance. These differences are detectable by research software, but may be too small to be perceived by the human eye (e.g. intervals <.02 sec or amplitudes <50 μv). Differences judged to be clinically significant, that is intervals ≥.02 sec or ≥50 μv, are indicated by a check mark in Table 6.

Results from analysis of the ten constructed dichotomous ECG criteria are displayed in Table 7. T wave inversion occurred in 44 (22%) of the SAH patients but in only 1 (3%) of the normal patients (p=.013). In addition, 48 (24%) patients in the SAH group met ECG criteria for LVH (p=.011).

During visual analysis for U waves, T-2 deflections were found on T waves in 12 patients in the SAH group and noted as a separate category. The T2 deflection is a clear large positive deflection superimposed on the end of the T wave, precluding measurement of its amplitude.

Discussion

This study quantified differences between ECG characteristics in normal patients and those with SAH. The shortening of both the PR interval and QRS complex durations is consistent with, and may provide additional support for the catecholamine hypothesis for etiology of ECG changes in SAH. Sympathetically mediated shortening of both the P

Table 7
Dichotomous ECG Variables

ECG Abnormality	Normal Group n=30 Frequency (%)	SAH Group n=200 Frequency (%)	p value*	Power (%)	Cramer's V
PR interval <120ms	1 (3%)	30 (15%)	.091	38	.115
QTc interval prolongation	2 (7%)	23 (12%)	.546	5	.052
ST elevation at J point	2 (7%)	4 (2%)	.177	18	.099
ST elevation at J+60	5 (17%)	31 (16%)	.793	2	.011
ST depression at J point	0	2 (1%)	1.000	1	.036
ST depression at J+60	0	1 (.5%)	1.000	1	.026
Inverted T waves	1 (3%)	44 (22%)	.013	79	.158
U waves elevation	0	19 (10%)	.145	14	.116
T-2 deflection	0	12 (6%)	.374	1	.091
LVH	0	48 (24%)	.011	99	.199

* Significance determined using Fisher's exact test

wave and PR interval have been demonstrated in several animal and human experiments (Damato et al., 1969; Irisawa & Seyama, 1966; Lepeschkin et al., 1960).

Moderate to very large differences in mean R and S wave amplitudes, as well as R wave areas, were found. Future research is required to determine the relationship between these differences and the frequent occurrence of LVH diagnosed by ECG among patients with SAH, and particularly the accuracy of ECG indicators of LVH in this population. By examining only one ECG tracing per patient, it was found that 24% of the SAH group in this study met standard ECG criteria for LVH.

Statistically significant differences in mean actual and absolute ST amplitude values occurred in eight of the 12 leads, indicating the need for further investigation into the prevalence and magnitude of ST deviation occurring in patients with SAH. T wave inversion is another striking feature in SAH compared to normal patients, and may provide an explanation for the large difference in T wave axis between the normal and SAH groups.

It may be noted that several cases of ST elevation and inverted T waves were detected in the normal group. This group was selected first by lack of cardiac-related diagnosis in the medical record, and secondly by screening of the initial ECG for very specific characteristics. This ECG screening was limited to BBB and LVH criteria, standard Q wave duration criteria for prior myocardial infarction, as well as characteristic early repolarization pattern. No specific screening was performed to eliminate all patients with ST deviation. Thus, patients having ST deviation, but none of these other conditions, were included in the normal group.

Limitations of the Study

This comparison study was limited chiefly by the small size of the only comparable group of normal subjects, that is, those in whom identical data acquisition and measurement techniques were used. While the study was sufficiently powered to demonstrate significant differences between continuous variables, this was not the case with dichotomous variables. As illustrated in Table 5, the sample size afforded sufficient power only in the case of T wave inversion and LVH. Nonetheless, results of this comparison have suggested several new variables that may prove useful in future studies of ECG abnormalities.

Conclusions

There are numerous differences in the ECGs of patients with SAH as compared to normal patients. Of particular interest are those affecting QRS complex amplitude, ST segment amplitude, and T wave direction and morphology. Further research is needed to determine the prevalence of such changes and their relationship to cardiac function and patient outcomes.

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Chapter 5: High Frequency of Cardiac Depolarization and Repolarization Abnormalities in Subarachnoid Hemorrhage: Evidence for the Catecholamine Hypothesis?

Subarachnoid hemorrhage (SAH) is a serious neurological disorder that may be complicated by the occurrence of electrocardiographic (ECG) abnormalities unexplained by preexisting cardiac conditions. These ECG changes may be misinterpreted as a problem that is primarily cardiac in nature, leading to delay in initiating appropriate interventions for SAH. Moreover, hearts of patients with brain death after SAH may be rejected for transplant because ECG abnormalities may be seen as indicative of coronary artery disease (CAD).

Prior investigations of ECG abnormalities in SAH have found a very wide range in reported prevalence rates. This discrepancy may be explained by differences in study designs, variation in sample size, and different definitions for ECG abnormalities. However, the number of ECGs analyzed and timing of ECG data collection in the clinical course may have a great influence on reported prevalence. Many prior studies have relied on small sample sizes with analysis of a single ECG. A few investigators performed serial ECGs, but none recorded tracings more than once daily. Because little is known about the timing or duration of ECG abnormalities in the clinical course of SAH, it is very possible that a single "snapshot" ECG tracing may miss changes. It is logical to assume that increasing the number of ECGs included in the analysis will improve the likelihood of capturing ECG abnormalities.

This descriptive, correlational study utilizes continuous 12-lead ECG monitoring, serial echocardiograms, and serum cardiac troponin I (cTnI) levels to investigate the

prevalence of selected ECG characteristics and abnormalities in patients admitted with aneurysmal SAH, and the relationship of these ECG changes to demographic, risk factor, disease severity, and outcome measures.

Materials and Methods

Sample and Setting

This study was part of an ongoing prospective investigation, Cardiac Response to Aneurysmal Subarachnoid Hemorrhage (CRASH). All consenting patients admitted with aneurysmal SAH to the neurological intensive care unit of a major academic medical center were included in this study. Patients with SAH of traumatic or infectious origin, or due to arteriovenous malformation were excluded.

Instruments and Procedures

ECG Data. Continuous 12-lead ECG recording commenced as soon as possible following admission and enrollment in the study, utilizing the Mortara ELI 100 ST Monitor (Mortara Instrument Inc., Milwaukee, WI). Ten adhesive skin electrode pads were applied to the patient, and lead wires from the Mortara ST monitor attached in standard Mason-Likar configuration (Mason & Likar, 1966). The Mortara ST monitor is a portable, programmable, microprocessor-based device, which samples electrical potentials from all 12 leads at 4ms intervals over a 10-second period to identify a noise-free median beat. From this median beat, the device measures ST segment deviation relative to the PR segment to a minimum resolution of 10μV.

The Mortara ST Monitor continuously monitors the patient's ECG, and stores tracings at preset intervals, as well as whenever a change in ST amplitude of 50μV (0.5mm) in one lead lasting more than one minute is detected. For this study, ECGs were

stored every 20 minutes, yielding a minimum of 72 ECGs stored for each patient per 24-hours of monitoring. Patients were monitored as continuously and for as long as possible during the neurological intensive care unit stay.

Continuous ECG data stored in the ST monitor were downloaded to the Mortara ST Review Station, a personal computer with additional ECG analysis software (Mortara Instrument, Inc. Milwaukee, WI). Recordings displaying artifact from muscle movement, electrode disruption, interference, or a pattern consistent with abrupt position change were eliminated from the downloaded ECG data. Questicus software (Inovise Medical, Inc., Newberg, OR) was used to present data recorded by the Mortara ST monitor in quantitative tabular form. This software displays ECG waveform amplitudes, including the ST segment, T wave, and QRS complex, in microvolt (μV) units for each of the 12 leads. Summary PR and QTc intervals and QRS duration for all 12 leads are measured in milliseconds (ms).

Because computerized measurement was not available for U wave amplitude, it was measured visually by the investigator, utilizing an ECG magnifying glass. Visual U wave detection was performed on the initial ECG recorded on every third day of monitoring for all patients. If U waves were detected using this technique, then for those patients, the first ECG recording on every day of monitoring was screened for occurrence of U waves. The same method was used to screen ECGs for T2 deflections, distinct positive waveforms on the downslope of the T wave, occurring before the T wave returns to the baseline (A. J. Moss, personal communication, February 28, 2003).

Selection of ECG Variables. ECG variables included in the analysis were selected based upon findings from a previously described pilot study (Sommargren, Zaroff, Banki,

& Drew, 2002). In that investigation, a single initial ECG from 100 patients with SAH showed one or more repolarization abnormalities (QTc interval prolongation, ST segment deviation, T wave inversion, or abnormal U wave) in 41% of patients. In addition, standard ECG criteria for LVH were met in 14% of patients.

Selection of ECG variables included in the current study was also guided by findings from a comparative analysis of ECGs recorded from patients with SAH and normal controls (Sommargren et al., 2003). In that study, we found significant differences between these two groups in the mean ST segment amplitude in eight of the 12 leads. PR interval duration was found to be significantly shorter in SAH patients than in normal controls, and T wave inversion occurred more frequently in those with SAH. In addition, 24% of patients with SAH had high QRS voltage that met ECG criteria for LVH.

Demographic and Clinical Data. As part of the parent CRASH study, patient demographics, history of cardiac risk factors, and Hunt Hess SAH grade upon admission were recorded. The Hunt Hess severity scoring system designates the degree of neurological impairment on admission, and ranges from 1, indicating minimal symptoms, to 5, indicating coma.

Patients in the CRASH study underwent transthoracic echocardiography on the first, third, and sixth day of enrollment in the study. For each echocardiographic study, a cardiac regional wall motion scoring index (RWMSI) was determined as a measure of left ventricular dysfunction. The RWMSI is produced by averaging the individual scores [1 (normal) – 3 (akinetic)] of 16 left ventricular segments. Left ventricular dysfunction was defined by a RWMSI>1.

The level of serum cTnI, a biomarker of myocardial cell death, was also

determined on the first, third, and sixth day of the study. A cTnI was considered elevated when it was >1.0μg/L, which is accepted as indicative of substantial myocardial necrosis at the study institution.

Statistical Analysis

All technically acceptable ECGs recorded during the study were included in the analysis. Individual ECG data files for each patient included 192 continuous ECG measurements and 11 dichotomous variables corresponding to specific ECG abnormalities identified as significant in our earlier studies. Definitions of ECG abnormalities are summarized in Table 8.

Results from the analysis of individual patients were incorporated into an aggregate database, which included 45 ECG variables, as well as demographic, risk factor, neurological status, and clinical outcome variables. Sample description, frequencies, and measures of central tendency were determined using descriptive statistics. The independent samples t test and Mann Whitney U test were used to explore associations between continuous variables and sample characteristics.

Univariate and multivariate logistic regression analyses were performed to determine which demographic (age, gender, ethnicity), risk factor (history of CAD, smoking, and hypertension), and disease severity (Hunt Hess SAH grade) variables were predictive of the five most prevalent ECG abnormalities. The same method was used to explore which ECG abnormalities were predictive of adverse outcomes, including elevated cTnI, abnormal RWMSI, and in-hospital all-cause mortality. Given the lowest sample size in these logistic regression models (n=202) using an alpha level of .05, there would be power of at least 80% to detect an adjusted odds ratio of at least 1.8.

Table 8
ECG Abnormality Operational Definitions

Variable Name	Definition
Short PR	≤120ms
Prolonged QTc	Males >450ms, females >460ms (Bazett's correction for heart rate)
Prolonged QRS duration	>120ms
High QRS amplitude	▪ R aVL >9mm(F), >11mm (M), *or* ▪ R aVL +S V_3 >20mm (F), >25mm (M), *or* ▪ S V_1 + R V_5 or R V_6 (whichever is taller) >35mm (age >35), *or* ▪ R V_6 > R V_5 (only if R V_5 & R V_6 >7mm) (Evans, 1997; Evans, 1999)
ST elevation at J	≥200μV in V_1 or V_2 or V_3 ,*or* ≥100μV in any other lead, measured at J point
ST elevation at J + 60	≥200μV in V_1 or V_2 or V_3 ,*or* ≥100μV in any other lead, measured 60ms after J point
ST depression at J	≥100μV in any lead, measured at J point
ST depression at J + 60	≥100μV in any lead, measured 60ms after J point
T inversion	Negatively deflected >100μV in any lead with predominantly positive QRS complex (excluding V_1 & V_2)
Prominent U wave	Separate positive wave after T wave and before next P wave >100μV
T2 deflection	Distinct positive waveform superimposed on downslope of T wave

Results

Sample Characteristics

Continuous 12-lead ECG data was recorded on a total sample of 227 patients admitted with aneurysmal subarachnoid hemorrhage. Patients enrolled in the study had a mean age of 55 years (range 17-90 years), and were predominantly female (68%). Ethnicity included white, 64%; Asian 14%; black, 9%; and Latino, 13%. Eighty-nine percent of patients in this sample were transferred from other hospitals, and mean Hunt-Hess grade was 2.33.

Forty-two percent of subjects had a history of hypertension, 45% had a history of smoking, and 8% had diabetes mellitus. There was a history of coronary artery disease in 4%, and a family history of coronary artery disease in 12%. Ten patients (4%) had bundle branch block (BBB) and one had early repolarization pattern. Serum cardiac troponin I was elevated in 19% of patients, brain death occurred in 3%, and all-cause mortality during hospitalization was 12%.

Analysis of ECG Data

Data from all 227 patients were analyzed for all selected variables, with several exceptions. Because BBB and normal variant early repolarization are most often chronic ECG patterns that are not associated with an acute event, such as SAH, and because they can cause artifactual deviation of the ST segment and T wave, patients with these conditions were excluded from the analysis of ST segment, T wave, and QRS complex abnormalities. Another condition that can distort the ST segment and T wave is left ventricular hypertrophy (LVH). Therefore, patients with persistent ECG evidence of LVH were excluded from ST segment and T wave frequency calculation. For this study,

persistent ECG evidence of LVH was defined as that occurring on ≥90% of ECG tracings.

Mean monitoring time for the 227 patients was 114 hours (range: .5 to 428 hours). A total of 89,430 technically acceptable ECGs were recorded, with a mean of 394 recordings per patient. In total, 223 patients (98%) had one or more ECG abnormality during monitoring. Frequencies of specific ECG abnormalities are summarized in Table 9.

Table 9
Frequency of ECG Abnormalities During Continuous 12-lead ECG Monitoring of Patients with Subarachnoid Hemorrhage

ECG Abnormality	Sample n	Frequency (%)
Short PR	227	152 (67)
Prolonged QTc	227	165 (73)
Prolonged QRS duration	217	33 (15)
High QRS amplitude	227	181 (80)
ST elevation at J	194	68 (35)
ST elevation at J+60	194	114 (59)
ST elevation at J or J+60	194	120 (62)
ST depression at J	194	87 (45)
ST depression at J+60	194	76 (39)
ST depression at J or J+60	194	96 (50)
T inversion	194	159 (82)
ST/T abnormality	194	174 (90)
Prominent U wave	227	45 (20)
T2 deflection	227	22 (10)

Abnormalities of the PR Interval

Enhanced atrioventricular nodal conduction was evident in 152 patients (67%) (PR interval <.12 sec). The mean minimum (shortest) PR interval was shorter in patients who had elevated cTnI levels (p=.037), abnormal RWMSI (p=.030), and among those who died (p=.027). These findings are summarized in Table 10.

Table 10
Shortest PR Interval Sample Mean: Differences Between Groups

	Mean shortest PR interval in milliseconds (standard deviation)
Normal serum cardiac troponin I	111 (±20.85)
Elevated serum cardiac troponin I	104 (±19.47)
Mean difference [95% CI]	7 [.45-14.9]
p	.037
Normal regional wall motion score index	111 (±20.20)
Abnormal regional wall motion score index	104 (±22.07)
Mean difference [95% CI]	7 [.70-13.41]
p	.030
Survived	111 (±20.28)
Died	102 (±22.98)
Mean difference [95% CI]	9 [1.08-17.48]
p	.027

Abnormalities of the QTc Interval

QTc interval was prolonged in 165 of the 227 patients (73%) (Figure 6). The mean maximum (longest) QTc interval duration recorded during the monitoring period was longer in female patients (p=.011), those with a history of hypertension (p=.023), elevated cTnI (p=.000), and abnormal RWMSI (p=.018) (Table 11).

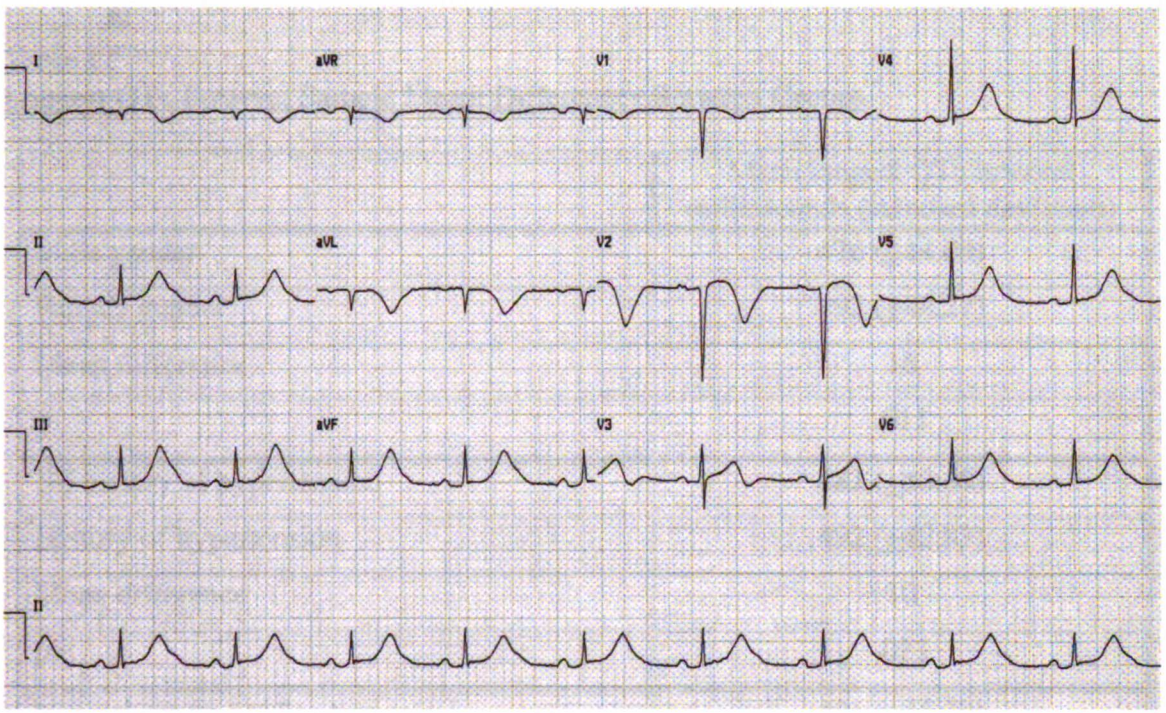

Figure 6. Prolonged QTc (596ms) in a 50 year old female patient with subarachnoid hemorrhage.

Table 11
Longest QTc Iinterval Sample Mean: Differences Between Groups

	Mean longest QTc interval milliseconds (standard deviation)
Male gender	476 (±44.09)
Female gender	492 (±48.27)
Mean difference	16
p	.011
No history of hypertension	482 (±50.40)
History of hypertension	492 (±42.83)
Mean difference	10
p	.023
Normal serum cardiac troponin I	481 (±45.79)
Elevated serum cardiac troponin I	511 (±48.41)
Mean difference	30
p	.000
Normal regional wall motion score index	483 (±47.95)
Abnormal regional wall motion score index	499 (±48.66)
Mean difference	16
p	.018

Abnormalities of the ST Segment and T Wave

A total of 194 patients without evidence of BBB or early repolarization pattern, or persistent ECG voltage evidence of LVH were included in the analysis of ST segment and T wave abnormalities. When measured at the J point, ST segment elevation occurred in 68 patients (35%). ST segment elevation occurred in 114 patients (59%) when

measured at J+60. Taken together, 120 (62%) had ST segment elevation at the J point, J+60, or both.

ST segment depression measured at the J point occurred in 87 patients (45%), while at J+60 it occurred in 76 (39%). ST segment depression at the J point or J+60 or both occurred in 96 (50%).

One hundred fifty-nine patients (82%) had inverted T waves (Figure 7). Of the 194 patients included in ST/T wave analysis, 174 (89%) had at least one ST/T wave abnormality (ST elevation and/or ST depression and/or inverted T waves) during the monitoring period.

Abnormalities of the U Wave

Of the total sample of 227 patients, 45 (20%) had prominent U waves (Figure 8). During visual analysis for U waves, T2 deflections were found on T waves in 22 patients (10%) and noted as a separate category (Figure 9). A T2 deflection is a clear large positive deflection superimposed on the downslope of the T wave, before it reaches the T-P baseline, thus precluding measurement of the T2 deflection amplitude.

Abnormalities of the QRS Complex

When the QRS complex duration was measured in the 217 patients without BBB upon enrollment into the study, 33 (15%) were abnormally prolonged some time during the monitoring period. It was longer among males, those with a history of CAD, but shorter among those who died during hospitalization (Table 12).

A total of 181 patients (80%) had higher than normal QRS amplitude mimicking LVH at least once during the monitoring period. However, in contrast to patients with

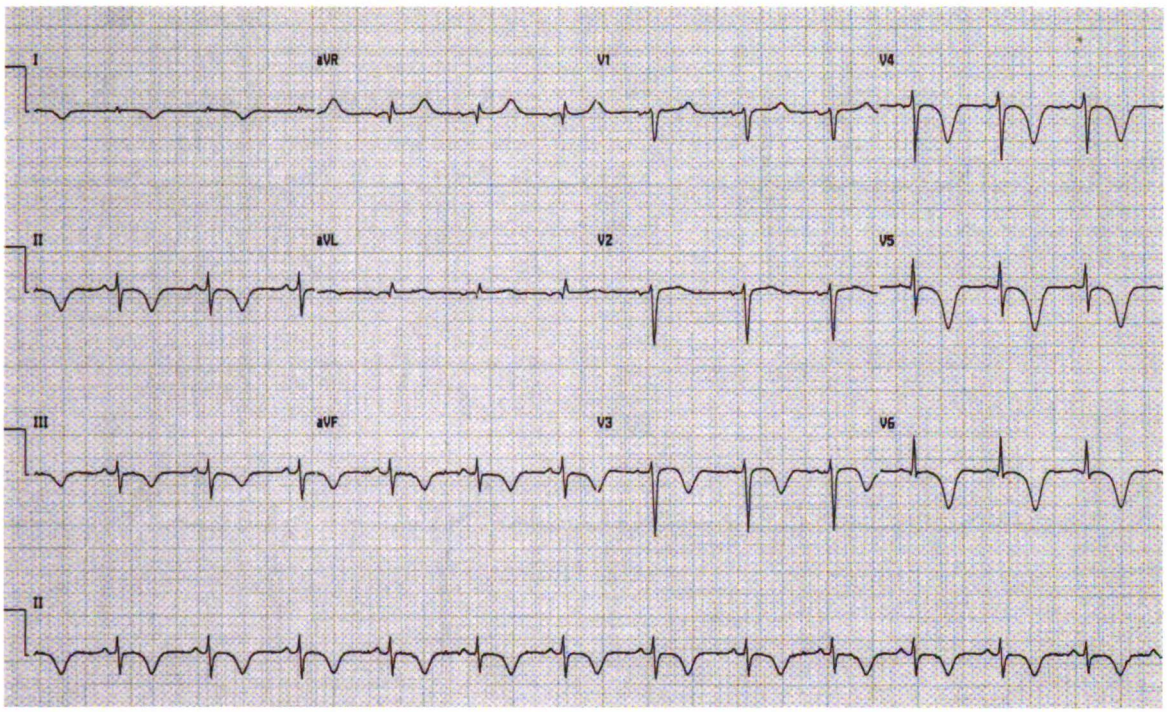

Figure 7. Inverted T waves (850μV) in lead V_6 in a 62 year old female patient with subarachnoid hemorrhage.

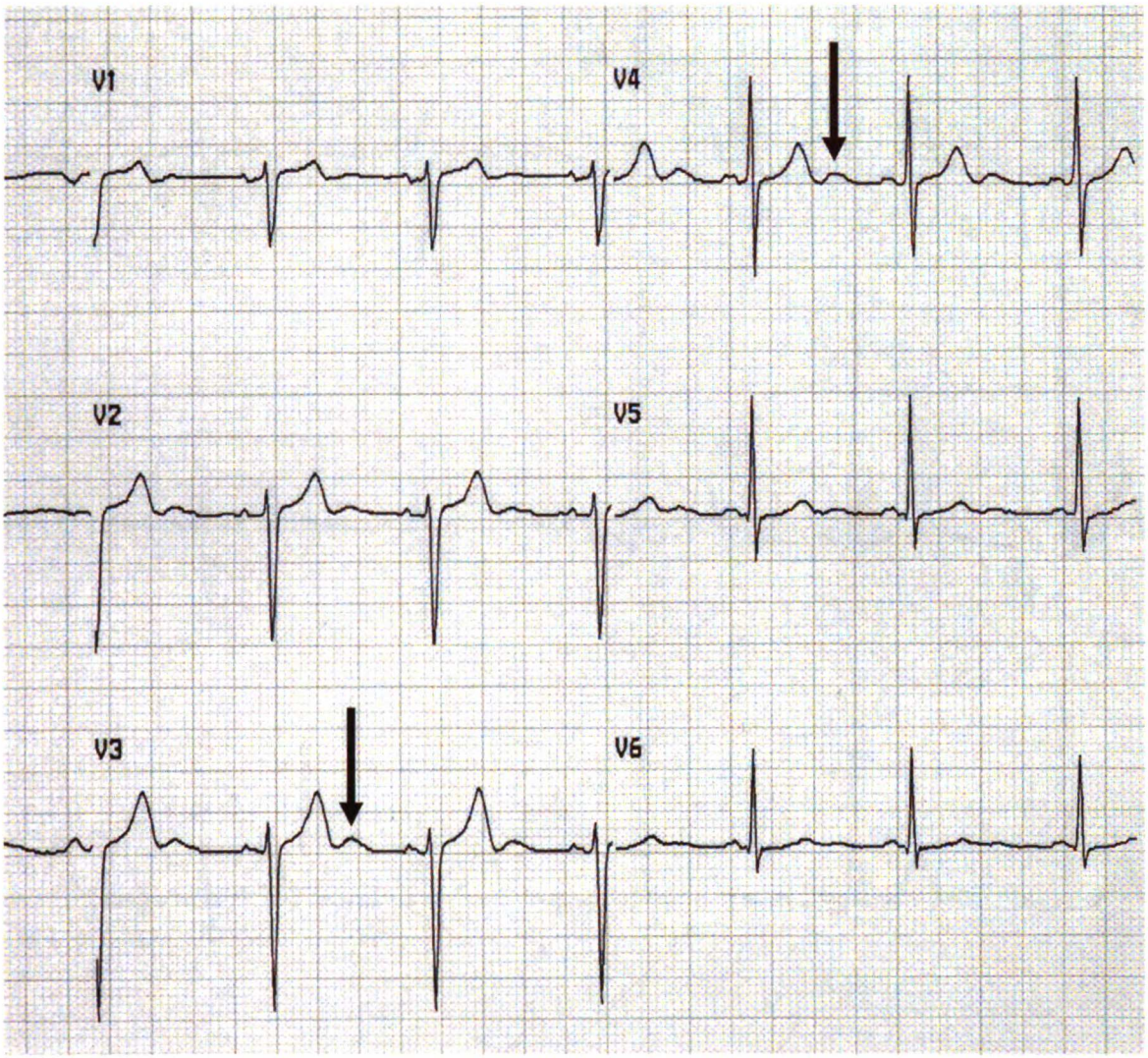

Figure 8. Prominent U wave (amplitude ≥100μV) in leads V_3 and V_4 in a 44 year old male patient with subarachnoid hemorrhage.

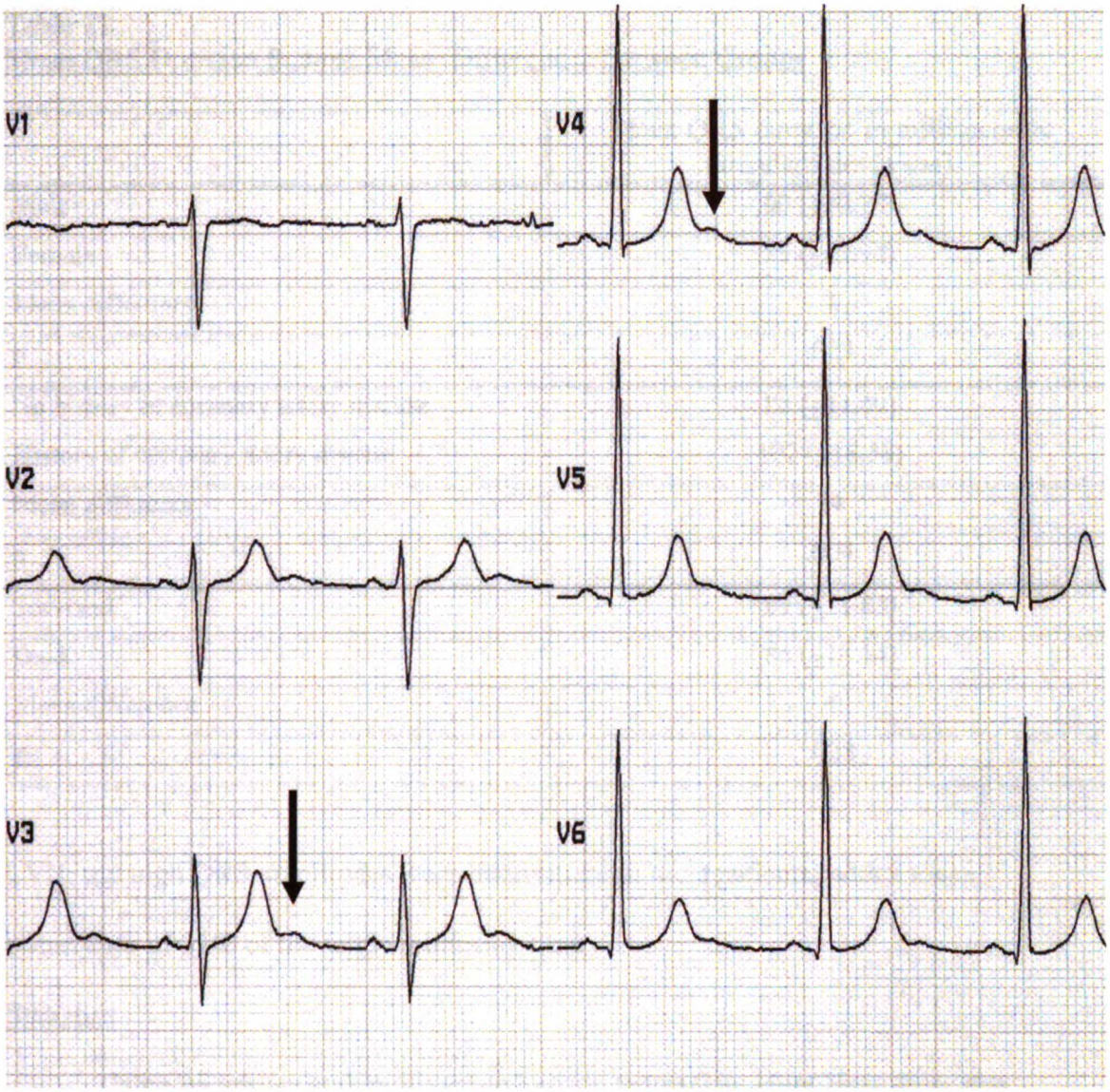

Figure 9. T2 deflections in leads V_3 and V_4 in a 40 year old male patient with subarachnoid hemorrhage.

Table 12
Mean QRS Duration Sample Mean: Differences Between Groups

	Mean QRS duration in milliseconds (standard deviation)
Male	90 (±10.20)
Female	88 (±12.94)
Mean difference	2
p	.023
No history of coronary artery disease	88 (±11.49)
History of coronary artery disease	102 (±18.38)
Mean difference	14
p	.004
Survived	89 (±11.83)
Died	85 (±18.14)
Mean difference	4
p	.028

LVH, the high QRS amplitudes were intermittent in most patients, with a mean occurrence of 31% of the total monitoring time.

Statistics

Using univariate and multivariate logistic regression, Hunt Hess score was predictive of a prolonged QTc interval (p=.008) (Table 13). Age, gender, ethnicity, and history of CAD were not predictive of the occurrence of any ECG abnormalities in this sample.

Logistic regression was also used to determine which ECG abnormalities were predictive of adverse patient outcomes, while controlling for demographic variables, risk factors, and Hunt Hess grade (Tables 14 through 16). A prolonged QTc interval was strongly predictive of elevated cTnI [OR 8.03 (95% CI 1.63-39.61), p=.011), and T wave

Table 13
Predictors for Prolonged QTc Interval; n=224 (excludes 3 patients without Hunt Hess score)

Predictor Variable	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p	OR	95% CI	p
Age	1.02	1.00-1.04	0.110	1.02	0.99-1.04	0.228
Female Gender	1.07	0.57-2.01	0.830	0.96	0.48-1.92	0.907
Ethnicity*			0.393			0.372
Black	2.31	0.64-8.30	0.199	2.92	0.77-11.07	0.115
Latino	0.78	0.33-1.81	0.554	0.78	0.32-1.93	0.592
Asian	1.52	0.61-3.76	0.370	1.20	0.44-3.30	0.720
History of CAD	1.52	0.31-7.38	0.602	2.27	0.43-11.97	0.334
History of hypertension	1.22	0.67-2.22	0.516	0.84	0.42-1.66	0.614
History of smoking	0.91	0.50-1.64	0.753	1.12	0.56-2.19	0.734
Hunt Hess grade†			0.008			0.008
Hunt Hess grade 2	1.24	0.54-2.83	0.609	1.30	0.55-3.08	0.550
Hunt Hess grade 3	3.74	1.63-8.59	0.002	3.96	1.65-9.50	0.002
Hunt Hess grade 4	3.24	1.21-8.62	0.019	3.39	1.25-9.22	0.017
Hunt Hess grade 5	4.52	0.53-38.43	0.167	5.54	0.63-48.45	0.122

*Caucasian race was the reference group
† Hunt Hess grade 1 was the reference group

Table 14
Predictors for Elevated Serum Cardiac Troponin I; n=219 (excludes 8 patients without Hunt Hess score and/or serum cardiac troponin I level)

Predictor Variable	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p	OR	95% CI	p
Age	1.01	0.99-1.04	0.330	0.99	0.96-1.04	0.985
Female Gender	2.56	1.07-6.12	0.034	4.45	1.51-13.14	0.007
Ethnicity*			0.814			0.514
Black	0.52	0.11-2.39	0.401	0.47	0.08-2.60	0.384
Latino	1.20	0.45-3.27	0.713	0.88	0.24-3.20	0.841
Asian	1.06	0.40-2.85	0.906	0.40	0.01-1.54	0.184
History of CAD	0.49	0.06-3.94	0.487	0.79	0.09-8.34	0.834
History of hypertension	1.28	0.65-2.55	0.477	1.00	0.42-2.15	0.994
History of smoking	0.69	0.34-1.40	0.310	0.60	0.32-1.88	0.295
Hunt Hess grade†			0.000			0.000
Hunt Hess grade 2	2.60	0.61-11.04	0.197	2.03	0.44-9.45	0.366
Hunt Hess grade 3	6.06	1.88-19.50	0.003	3.92	1.11-13.17	0.033
Hunt Hess grade 4	9.73	2.87-32.96	0.000	9.10	2.42-34.17	0.001
Hunt Hess grade 5	58.40	8.83-386.23	0.000	120.07	11.38-1267.26	0.000
Short PR	2.62	1.10-6.27	0.030	1.72	0.58-5.06	0.328
Prolonged QTc	9.11	2.12-39.06	0.003	8.03	1.63-39.61	0.011
ST segment elevation	1.11	0.54-2.28	0.774	1.31	0.53-3.25	0.557
ST segment depression	1.31	0.66-2.613	0.447	0.60	0.24-1.50	0.274
T wave inversion	2.89	0.84-9.94	0.092	4.09	0.80-20.94	0.091

*Caucasian race was the reference group
† Hunt Hess grade 1 was the reference group

Table 15
Predictors for Abnormal Regional Wall Motion Score Index; n=202 (excludes 25 patients without Hunt Hess score and/or regional wall motion score index)

Predictor Variable	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p	OR	95% CI	p
Age	0.99	0.97-1.01	0.309	0.98	0.95-1.00	0.092
Female Gender	1.78	0.89-3.55	0.103	3.10	1.34-7.20	0.008
Ethnicity			0.353			0.122
Black	1.76	0.63-4.91	0.280	1.91	0.56-6.58	0.303
Latino	1.84	0.76-4.49	0.179	3.22	1.06-9.74	0.039
Asian	0.81	0.32-2.04	0.650	0.81	0.26-2.51	0.711
History of CAD	0.70	0.14-3.47	0.661	0.79	0.14-4.57	0.794
History of hypertension	0.99	0.53-1.84	0.970	0.98	0.45-2.13	0.966
History of smoking	1.61	0.871-2.97	0.129	2.32	1.06-5.08	0.034
Hunt Hess grade†			0.025			0.007
Hunt Hess grade 2	1.05	0.36-3.03	0.934	0.58	0.18-1.93	0.376
Hunt Hess grade 3	2.56	1.15-5.71	0.021	2.62	1.04-6.60	0.041
Hunt Hess grade 4	2.91	1.19-7.08	0.019	3.36	1.21-9.33	0.020
Hunt Hess grade 5	5.81	1.17-28.94-	0.032	12.17	1.79-82.62	0.011
Short PR	2.71	1.27-5.81	0.010	2.35	0.95-5.79	0.064
Prolonged QTc	2.40	1.08-5.30	0.031	1.57	0.62-3.95	0.342
ST segment elevation	1.16	0.61-2.21	0.652	0.92	0.42-2.01	0.825
ST segment depression	1.07	0.58-1.98	0.826	0.64	0.29-1.40	0.260
T wave inversion	3.25	1.09-9.74	0.035	4.43	1.20-16.45	0.026

*Caucasian race was the reference group
† Hunt Hess grade 1 was the reference group

Table 16
Predictors for In-Hospital Mortality; n=224(excludes 3 patients without Hunt Hess score)

Predictor Variable	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p	OR	95% CI	p
Age	1.04	1.01-1.07	0.020	1.05	1.01-1.09	0.020
Female Gender	0.81	0.36-1.87	0.626	0.55	0.20-1.55	0.257
Ethnicity			0.816			0.973
Black	0.00		0.744	0.00		0.755
Latino	1.11	0.35-3.56	0.859	1.27	0.30-5.39	0.746
Asian	1.60	0.58-4.43	0.363	1.20	0.30-4.92	0.803
History of CAD	0.77	0.09-6.32	0.807	0.93	0.07-11.77	0.955
History of hypertension	1.64	0.74-3.63	0.224	1.10	0.40-3.06	0.851
History of smoking	0.79	0.35-1.78	0.576	1.09	0.36-3.29	0.882
Hunt Hess grade†			0.000			0.001
Hunt Hess grade 2	2.48	0.34-18.37	0.373	3.21	0.37-27.72	0.288
Hunt Hess grade 3	7.09	1.47-34.12	0.015	9.44	1.55-57.60	0.015
Hunt Hess grade 4	15.76	3.24-76.58	0.001	18.61	3.09-11.95	0.001
Hunt Hess grade 5	68.30	9.21-506.63	0.000	86.66	8.77-856.67	0.000
Short PR	2.56	0.93-7.02	0.069	2.82	0.76-10.45	0.120
Prolonged QTc	1.84	0.67-5.08	0.239	0.92	0.27-3.19	0.897
ST segment elevation	1.07	0.47-2.44	0.875	1.51	0.52-4.39	0.447
ST segment depression	2.60	1.10-6.19	0.030	2.26	0.74-6.87	0.153
T wave inversion	0.93	0.33-2.63	0.893	0.21	0.05-0.93-	0.039

*Caucasian race was the reference group
† Hunt Hess grade 1 was the reference group

inversion was shown to be predictive of abnormal RWMSI [OR 4.43 (95% CI 1.20-16.45), p=.026]. No ECG abnormalities were predictive of mortality when demographic factors, history, and disease severity were included in the analysis.

Discussion

This study is the first to use continuous 12-lead ECG monitoring to investigate the prevalence of ECG abnormalities in patients with SAH. Previous studies have reported a wide range of prevalence, ranging from 47% (Salvati et al., 1992) to 100% (Brouwers et al., 1989; Goldstein, 1979), and some of this variation may be explained by the frequency of ECG recordings. Most of these investigations included only one 12-lead ECG recording per patient (Melin & Fogelholm, 1983; Rudehill, Olsson, Sundqvist, & Gordon, 1987), while others relied on several ECG tracings per patient, sometimes recorded at irregular or unspecified intervals (Kreus, Kemilä, & Takala, 1969; Salvati et al., 1992). Twelve-lead ECG data were collected in a consistent manner over a substantial period of time in only three past investigations (Brouwers et al., 1989; Cruickshank., Neil-Dwyer, & Brice,1974; Eisalo, Peräsalo, & Halonen, 1972). Even these, however, were limited by the snapshot approach of intermittent ECG recording, which reflects the ECG status only for the 10 seconds during which the recording is taking place. A few investigators have utilized 24-hour Holter recordings, but these were limited to only two ECG leads.

Our continuous 12-lead ECG investigation, which recorded a mean of 394 ECGs per patient over a mean monitoring time of 114 hours, demonstrated higher prevalence rates for most of the included ECG abnormalities than any previous study. Computer-assisted measurement, used for all waveforms and intervals except for U waves and T2 deflections, made possible the inclusion of all 89,430 technically acceptable ECGs

recorded during the study period. This also provided more accurate measurement than is possible by visual examination and is free from human bias.

The mechanism for myocardial damage after SAH is theorized to occur when sympathetic stimulation results in the release of the catecholamine norepinephrine from local sympathetic nerve endings in the heart, causing pinpoint or "buckshot" patterns of damage (Drislane, Samuels, Kozakewich, Schoen, & Strunk, 1987; Greenhoot & Reichenbach, 1969). This necrosis has been demonstrated to occur in the distribution of the cardiac nerves, rather than the regional involvement seen in cardiac damage due to CAD. For this reason, the requirement for ST deviation and T wave inversion occurring in two or more contiguous leads has not been extended to the SAH population.

Our findings of very high prevalence of shortened PR and prolonged QTc interval durations, as well as their association with elevated cTnI and abnormal RWMSI, provides additional support for the catecholamine hypothesis for etiology of ECG changes in SAH. These sympathetically mediated ECG changes have been demonstrated in several animal and human experiments (Damato et al., 1969; Irisawa & Seyama, 1966; Lepeschkin et al., 1960). In addition, excessive sympathetic outflow has been proposed as a major causative factor of myocardial wall motion abnormalities after SAH (Zaroff, Rordorf, Ogilvy, & Picard, 2000).

The rate of high QRS amplitude, detected by applying standard ECG criteria for LVH, is extraordinarily high (80%). Perhaps even more unexpected is the transient nature of these QRS changes in the majority of cases. Further investigation, specifically study of the accuracy of ECG diagnostic criteria for LVH compared with echocardiographic evidence of LVH, is needed to elucidate these findings.

The identification of prolonged QTc interval as an independent predictor of elevated cTnI, and T wave inversion as highly predictive of abnormal RWMSI, may assist clinicians in recognizing those patients who are at higher risk for myocardial damage and dysfunction.

Limitations of the Study

The prevalence of ECG abnormalities may be higher than reported in this study, because the period immediately after onset of SAH symptoms, during which ECG abnormalities have been reported to occur most frequently, were not monitored in many of the patients. A total of 71 patients (31%) were monitored during the first 72 hours after onset of SAH symptoms. Several prior studies of ECG abnormalities after SAH have found the highest prevalence in the first 24 to 72 hours after SAH onset (Brouwers et al., 1989, Di Pasquale et al., 1987). Because SAH occurs in only 30,000 persons annually in the United States (US Health and Human Services), only tertiary care centers admit a sufficient volume of patients with SAH to conduct prevalence studies such as this. Most of the patients in the study were transferred from other facilities, and were admitted to the study institution on the second or third day after the onset of symptoms. Nevertheless, we found an extraordinarily high rate of ECG changes in our patient sample.

Changes in ECG morphology due to body position change have been well documented (Adams & Drew, 1997; Drew & Adams, 2001; Sutherland et al., 1983). This introduces the possibility that body position change may have caused some abnormalities in ECG morphology. However, to avoid inclusion of ECGs distorted by body position change, ECG data were visually screened for patterns characteristic of electrode disruption, interference, or abrupt position change, and any such recordings were

eliminated from the analysis.

This study did not include analysis of ECGs recorded prior to SAH. Ideally, comparison of pre- and post-SAH ECGs could differentiate pre-existing abnormalities from those truly associated with SAH. However, because patients in the present study were relatively young and in good general health, with 96% of patients having no coronary artery disease by history, it is highly unlikely that such a high prevalence of ECG abnormalities existed prior to SAH.

Conclusions

ECG abnormalities occur in a high proportion of patients with SAH during the acute phase. These ECG abnormalities include: (1) short PR interval; (2) prolonged QTc interval; (3) high QRS amplitude; (4) ST segment deviation; (5) T wave inversion; and (6) prominent U waves. High QRS amplitude mimicking LVH occur in most patients, but, unlike the case of chamber hypertrophy, are largely transient. Prolonged QTc after SAH is significantly related to myocardial injury, and T wave inversion is highly predictive of myocardial dysfunction. ECG abnormalities are not predictive of all-cause in-hospital mortality among patients with SAH.

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Chapter 6: Electrocardiographic Abnormalities in Patients with Aneurysmal Subarachnoid Hemorrhage: Timing and Duration in the Clinical Course

Subarachnoid hemorrhage (SAH) is a catastrophic neurological event caused most often by rupture of an aneurysm at the base of the brain. In addition to neurological signs and symptoms, electrocardiographic (ECG) abnormalities, unrelated to pre-existing coronary artery disease (CAD), are frequently reported. Previous studies have found prevalence of these abnormalities ranging from 47% to 100% (Brouwers et al., 1989; Salvati et al., 1992; Sommargren et al., 2003a), but few investigations have included the duration of ECG abnormalities or their timing after SAH. This lack of data on duration and timing is largely due to the frequency and length of ECG data collection. Most past investigations obtained data from one to several "snapshot" ECGs. None have obtained continuous 12-lead ECGs on patients with SAH, and those looking at serial tracings recorded on a systematic basis are few. Therefore, it remains unclear whether observed ECG abnormalities are transient or permanent.

This prospective, descriptive study utilizes continuous 12-lead ECG data recorded on SAH patients during the intensive care unit stay to determine timing of ECG abnormalities during the clinical course and their duration.

Materials and Methods

Sample and Setting

All consenting patients admitted with aneurysmal SAH to the neurological intensive care unit of a major academic medical were enrolled in an ongoing prospective investigation, Cardiac Response to Aneurysmal Subarachnoid Hemorrhage (CRASH). As part of this

study, a previous investigation used continuous 12-lead ECG data to determine the prevalence of ECG abnormalities while the patient was in intensive care (Sommargren et al., 2003a). For the current investigation, data from patients who were found in the prevalence study to have any ECG abnormalities were further analyzed to determine the timing and duration of these abnormalities. All technically acceptable ECG data from all patients with ECG abnormalities were included in this analysis, with the exception of the ST segment and T wave portion of the analysis. Because several chronic ECG patterns, including bundle branch block (BBB), early repolarization, and left ventricular hypertrophy (LVH), can alter the morphology of the ST segment and T wave, patients exhibiting these patterns were excluded from ST segment and T wave analyses.

Instruments and Procedures

ECG Data. Continuous 12-lead ECG monitoring was begun immediately after enrollment to the study. Ten adhesive skin electrodes were applied to the patient in standard Mason-Likar configuration (Mason & Likar, 1966), and attached via lead wires to the Mortara ELI 100 ST Monitor (Mortara Instrument, Inc., Milwaukee, WI). The Mortara monitor, a portable, programmable, microprocessor-based device, samples electrical potentials from all 12 leads at 4ms intervals over a 10-second period to identify a noise-free median beat. The device uses this median beat to measure ST segment deviation relative to the PR segment to a minimum resolution of 10μv.

The Mortara instrument monitors the patient's ECG continuously and stores data at preset intervals; for this investigation, ECG data were stored at 20 minute intervals. In addition, the monitor records ECG data whenever an ST segment amplitude change of 50μv (0.5mm) occurs in one lead and lasts more than one minute. This resulted in a

minimum of 72 ECG recordings for each patient for each 24 hour period. Patients were monitored for as long as possible and as continuously as possible while in the intensive care unit.

Data from the Mortara monitor were downloaded to the Mortara ST Review Station, a personal computer with ECG analysis software (Mortara Instrument, Inc., Milwaukee, WI). ECG data were then visually screened by one of the investigators (CS) to eliminate artifact from muscle movement, electrode displacement, or a pattern consistent with abrupt position change. Data were further processed using Questicus software (Inovise Medical, Inc., Newberg. OR) to produce a spreadsheet format displaying quantitative ECG measurements, including the ST segment, T wave, and QRS complex in microvolt (μv) units for all 12 leads, and summary PR and QTc intervals and QRS duration for all 12 leads in millisecond ms) units.

Amplitudes of U waves were measured visually by one of the investigators (CS) using an ECG magnifying glass, because computerized U wave measurement is not available. The first technically acceptable ECG after enrollment was visually screened for U waves, followed by the first ECG on every third day of monitoring. If any U waves were found using this method, then the first ECG of every 24 hour period of monitoring was also screened. T2 deflections, which are positive waveforms on the downslope of, but not separate from, the T wave (A.J. Moss, personal communication, February 28, 2003), were detected using the same visual screening technique.

Selection of ECG Variables. ECG abnormalities were selected for this study based on results of both a pilot study (Sommargren, Banki, Zaroff, & Drew, 2002) and a comparative analysis of ECGs recorded from patients with SAH and normal controls

(Sommargren et al., 2003b). Selected variables included: shortened PR interval [<120ms (.12sec)]; prolonged QTc interval [>450ms (.45sec) in males or >460ms (.46sec) in females]; ST segment elevation [≥200μV (2mm) in V_1, V_2, or V_3, or ≥100μV (1mm) in any other lead] measured both at the J point and at 60ms after the J point (J+60); ST segment depression [≥100μV (1mm) in any lead] measured both at the J point and at J+60; T wave inversion [negatively deflected, ≥100μV (1mm) in any lead with predominantly positive QRS complex, excluding V_1, and V_2]; abnormal U waves [separate from T wave, ≥100μV (1mm) in any lead]; and T2 deflections.

Demographic Data. Patient demographics, risk factors, and Hunt Hess SAH grade were recorded upon enrollment in the CRASH study. Risk factors included history of CAD, hypertension, and smoking. The Hunt Hess SAH grade is a classification system used to designate the severity of neurological impairment upon admission to the hospital. Scores range from 1, designating minimal or no symptoms, to 5, designating deep coma (Hunt & Hess, 1968).

Statistical Analysis

Sample description, frequencies, and measures of central tendency were determined using descriptive statistics. To determine the time of occurrence of ECG abnormalities during the course of illness, the presence or absence of specific ECG abnormalities was ascertained for each patient. These dichotomous ECG data were sorted by day after SAH, with the day of onset of SAH symptoms designated as Day 1, and each subsequent day divided into two 12-hour blocks, (i.e. second day 12 a.m. to 11:59a.m. = Day 2.0, second day 12 p.m. to 11:59 p.m. = Day 2.5, third day 12 a.m. to 11:59 a.m. = Day 3.0, etc.). Frequencies reflect the occurrence of an abnormality in at least one lead at

least once during the 12 hour time period. The sorted data was then used to determine frequency of occurrence of ECG abnormalities for each time period in the entire sample.

To determine the duration of ECG abnormalities during the intensive care unit stay, descriptive statistics were used to calculate the mean and maximum number of consecutive time periods during which the ECG abnormality occurred in the sample.

Results

Sample Characteristics

A total of 223 patients were included in the study. The mean age of patients was 55 years (range 17-90 years) and 68% were female. The sample reflected the racial mix characteristic of the geographic region, with 64% white, 14% Asian, 13% Latino, and 9% black. The majority of patients (89%) were transferred to the study institution from other hospitals, and the mean Hunt Hess grade was 2.4.

Analysis of risk factors determined history of CAD in 5% and family history of CAD in 12%. Forty-two percent had a history of hypertension, 44% had a history of smoking, and 8% had a history of diabetes. Of the patients in this sample, 19% had elevated serum cardiac troponin I, a biomarker of myocardial injury, 28% had abnormal cardiac regional wall motion score index, a measure of left ventricular dysfunction. Brain death occurred in 3%, and all cause mortality during hospitalization was 13%.

The mean number of ECG recordings per patient was 399, and mean monitoring time was 115 hours (range .5 to 428 hours). A total of 88,972 technically acceptable ECGs were recorded and included in the analysis. In this study, as in earlier prevalence study, we excluded 33 patients from ST segment deviation and T wave inversion analyses because of early repolarization pattern (n=1), BBB (n=10), and ECG evidence consistent with LVH (n-=24). Some patients in this group had more than one of these conditions.

Timing of ECG Abnormalities of PR and QTc Intervals, U Wave, and T2 Deflection

A total of 223 patients were monitored for the frequency on each SAH Day of shortened PR interval, prolonged QTc interval, U wave, and T2 deflection. The number of patients being monitored on each SAH Day was lowest on SAH Day 2 (n=10), gradually increased and peaked on SAH Day 8.0 (n=133), then decreased until SAH Day 20.5 (n=11) (Figure 10). For statistical stability, time periods having fewer than 10 patients being monitored were excluded from the analysis. This resulted in data ranging from SAH day 2 to 20.5. SAH Day 1 was excluded because data were recorded on only two patients on that day. At the high end of the range, data from several patients monitored after SAH Day 20.5 and one patient monitored up to SAH Day 28 were excluded. Percentages of patients in whom ECG abnormalities occurred are calculated on the number monitored for each time period.

PR interval shortening. The frequency of PR interval <120ms (.12sec) gradually increased from SAH Day 2.0 (10%) and occurred most frequently on SAH Day 12 (65%), followed by a gradual decrease in frequency for monitoring days later in the clinical course (Figure 11). However, PR interval shortening persisted in greater than 25% of patients monitored through SAH Day 20.

QTc interval prolongation. The frequency of prolongation of the QTc interval remained relatively constant in the range of 30 to 40% for most SAH Days analyzed, but increased on SAH Day 14 (Figure 12). The greatest frequency of QTc prolongation occurred on SAH Day 16.5, when it occurred in 60.7% of patients monitored on that day.

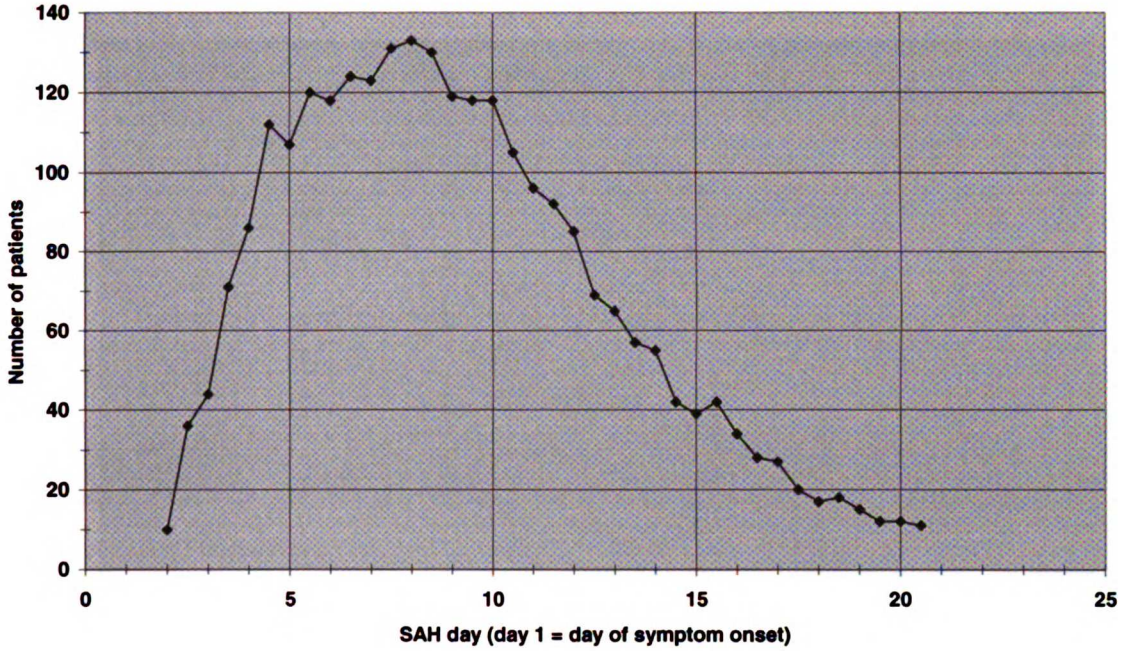

Figure 10. Number of patients monitored on each SAH Day for short PR interval, prolonged QTc interval, U wave, and T2 deflection. Total n=223.

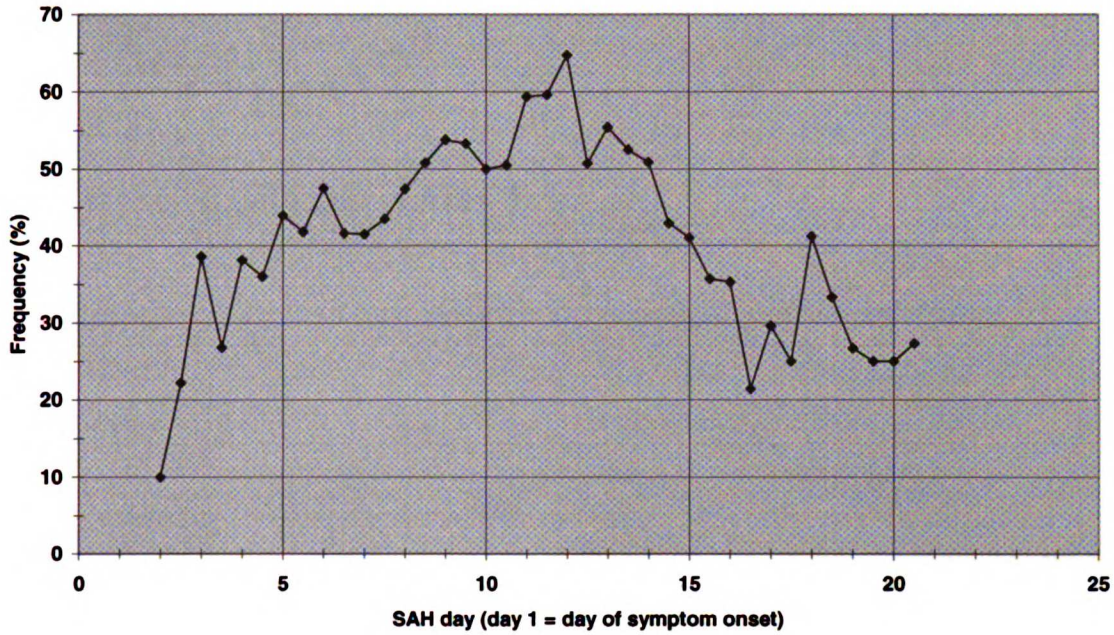

Figure 11. Frequency (%) of short PR interval [<120ms (.12sec)] on each SAH Day (n is different for each SAH Day - see Figure 10).

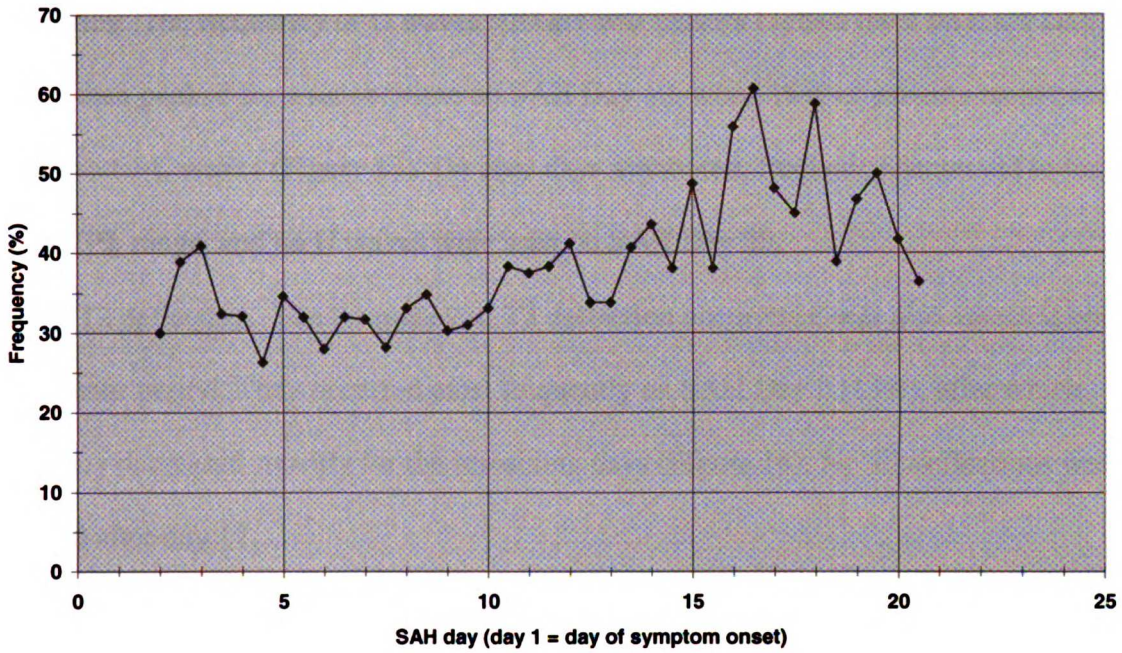

Figure 12. Frequency (%) of prolonged QTc interval [>450ms (.45sec) in males and >460ms (.46sec) in females] on each SAH Day (n is different for each SAH Day - see Figure 10).

U wave elevation. U waves were assessed only once in each 24 hour period of monitoring. The frequency of U waves >100μv was near its highest level on SAH Day 2 (17%), then peaked for a second time on SAH Day 10, when 18% of patients monitored had elevated U waves (Figure 13). On later days monitored, frequency decreased to the 4% to 13% range, and no U waves were seen on SAH Day 20.

T2 deflection. The frequency of T2 deflection occurrence was also assessed once per 24 hour period. They occurred most frequently on SAH Day 2 (13%), after which frequency decreased steadily for the remaining days (Figure 14). No T2 deflections were detected after day 17.

Timing of ECG Abnormalities of ST Segment and T Wave

After exclusion of patients with ECG patterns consistent with BBB, LVH, and early repolarization, a total of 190 patients was included in the analysis of the timing during the clinical course of ST elevation, ST segment depression, and T wave inversion. As with the earlier analyses, time periods having fewer than 10 patients being monitored were excluded. This resulted in data ranging from SAH day 2.5 to 20.5.The number of patients monitored on each SAH Day gradually increased from SAH Day 2.5 (n=28), with the greatest number of patients monitored on SAH Day 8.0 (n=117). Subsequently, the number of patients decreased until SAH Day 20.5 (n=10) (Figure 15).

ST segment elevation. When measured at the J point, the frequency of ST elevation occurred in a relatively irregular pattern, generally ranging from 3% to 12% with several peaks of increased occurrence on SAH Days 2.5 (18%), 13 (20%), and 17.5 (25%) (Figure 16).

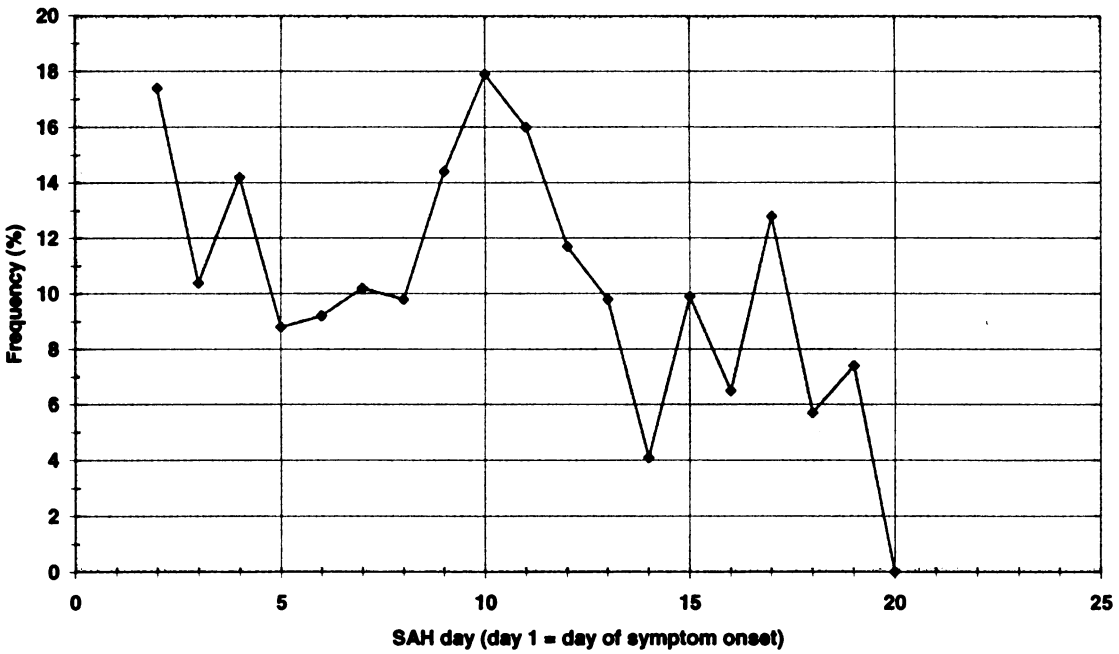

Figure 13. Frequency (%) of elevated U wave [>100μv (1mm)] on each SAH Day (n is different for each SAH Day - see Figure 10).

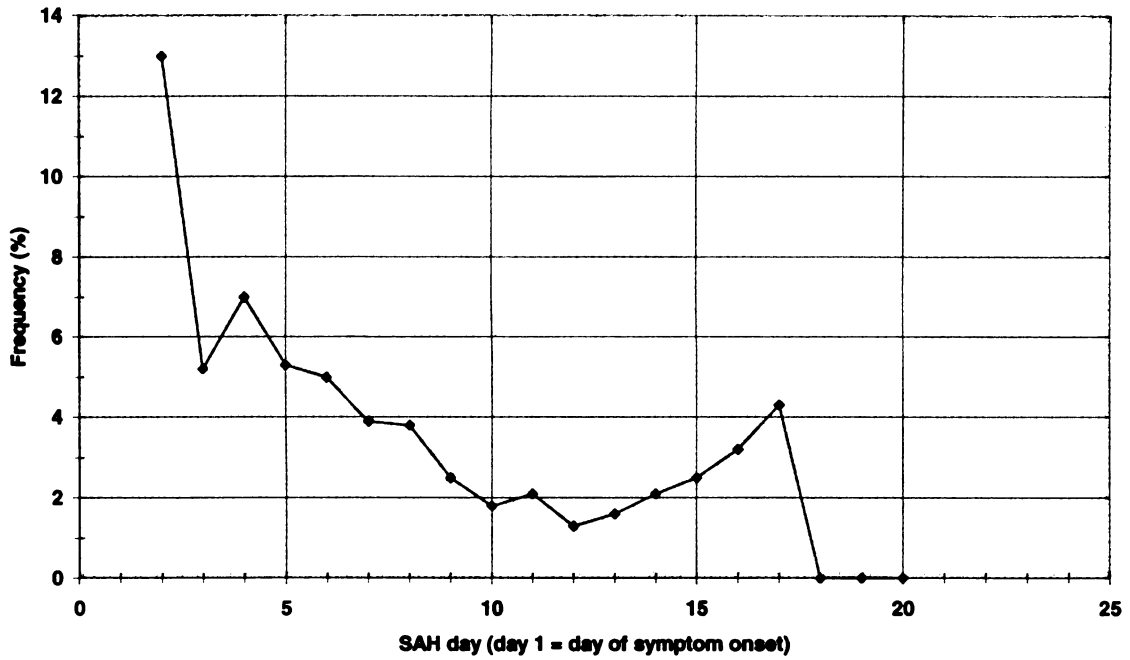

Figure 14. Frequency (%) of occurrence of T2 deflection on each SAH Day (n is different for each SAH Day - see Figure 10).

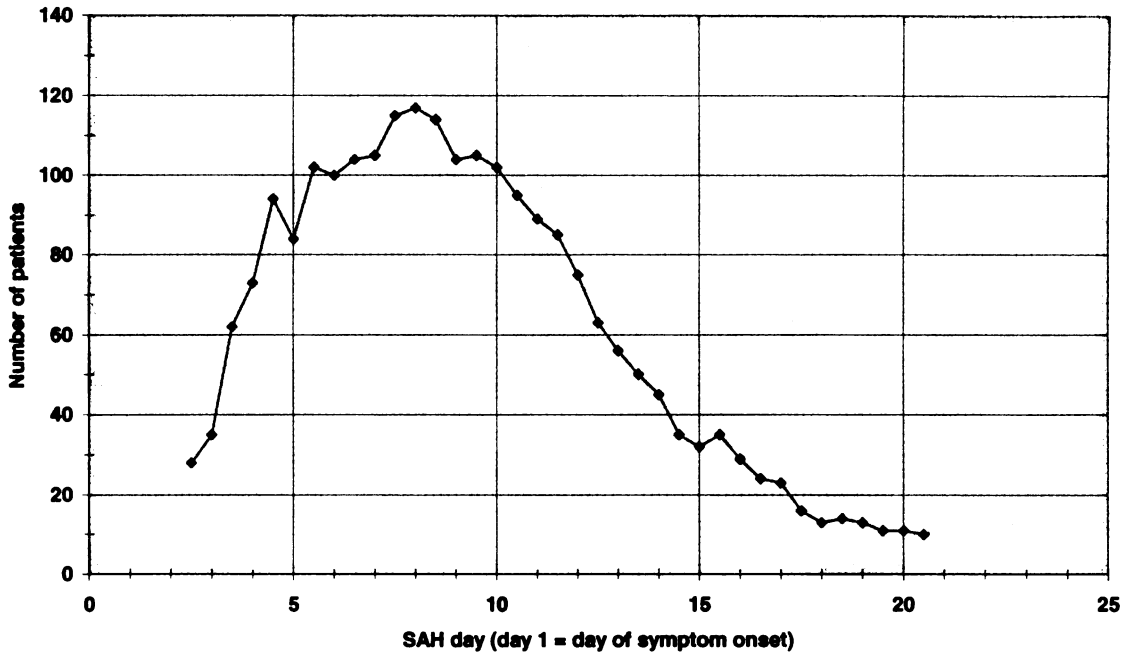

Figure 15. Number of patients monitored on each SAH Day for ST segment elevation, ST segment depression, and T wave inversion. Total n=190. Excludes patients with ECG patterns consistent with bundle branch block, early repolarization, and left ventricular hypertrophy.

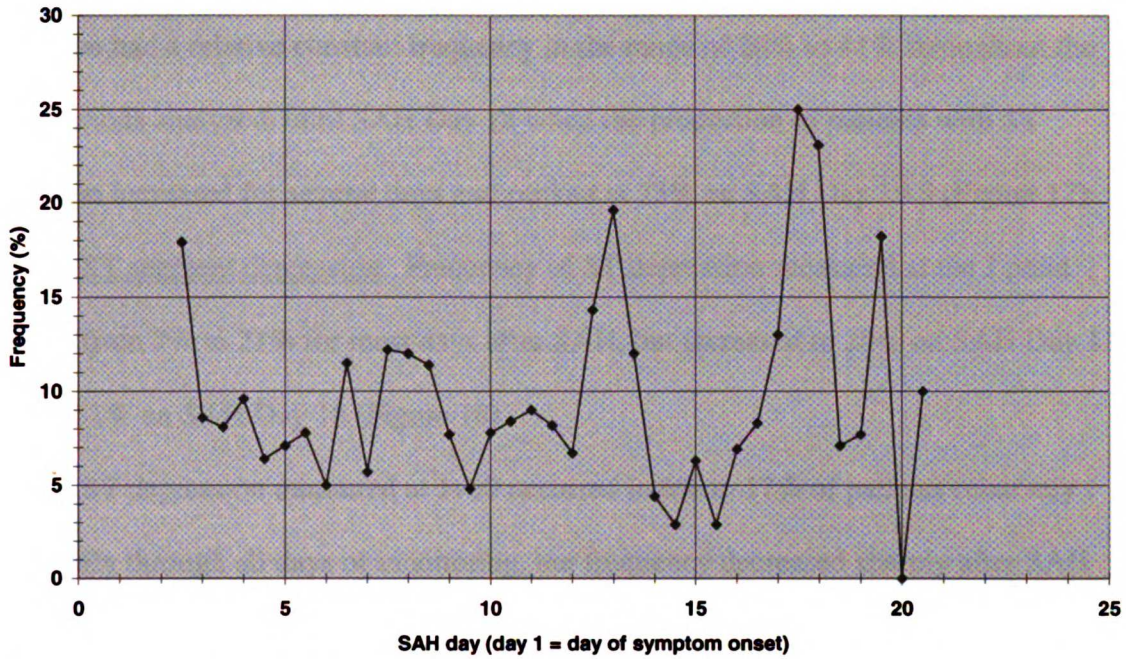

Figure 16. Frequency (%) of ST segment elevation measured at the J point [≥200μV (2mm) in V_1, V_2, or V_3, or ≥100μV (1mm) in any other lead] on each SAH Day (n is different for each SAH Day - see Figure 15).

When ST elevation was measured at 60ms after the J point (J+60), ST segment elevation had a relative constant frequency in the range of 20% to 41% throughout the time periods analyzed, until SAH Day 18 when the proportion of patients with ST elevation increased for several days and peaked at 73% on SAH Day 19.5 (Figure 17).

ST segment depression. Frequency of ST depression measured at the J point ranged from 7% to 21% for most days after SAH, but increased to 29% on SAH Day 13.5 and to 31% on SAH Day 18 (Figure 18).

ST depression measured at J+60 occurred in 6% to 17% of patients relatively constantly through all days of monitoring, but frequency decreased sharply after SAH Day 17 (Figure 19).

T wave inversion. The proportion of patients with T wave inversion remained fairly high throughout all monitoring days. The frequency gradually and consistently increased as the days of monitoring progressed, from 31% on SAH Day 3.0 to a peak of 93% on SAH Day 18.5 (Figure 20).

Duration of ECG Abnormalities

The mean and maximum number of consecutive time periods during which each specific ECG abnormality persisted was calculated from the total number of patients who had at least one occurrence of the abnormality. Seven patients who were monitored during only one time period were excluded from this analysis. Results are reported in Table 1.

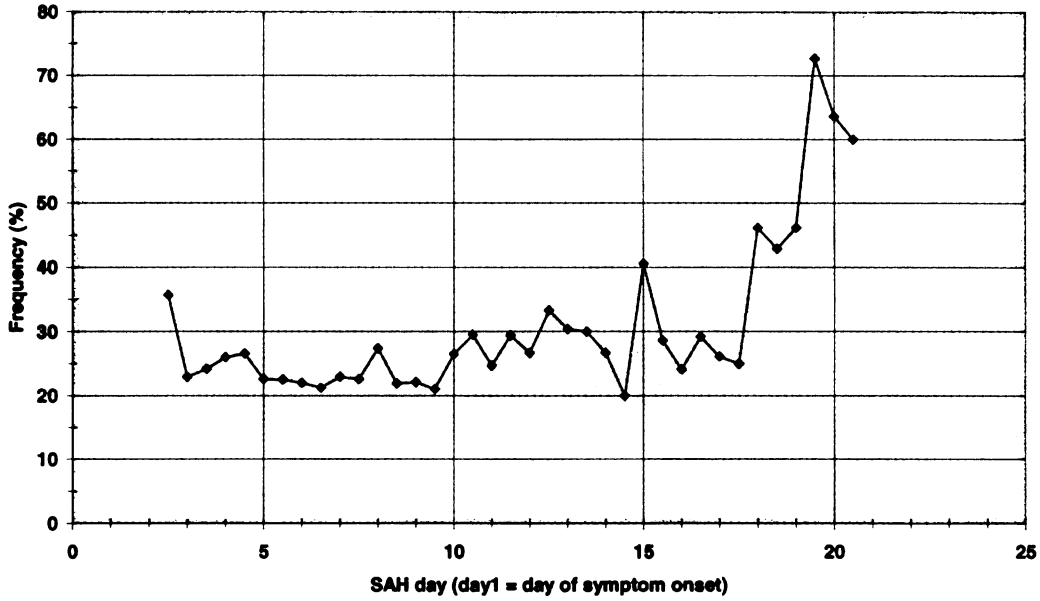

Figure 17. Frequency (%) of ST segment elevation measured at 60ms after the J point [≥200μV (2mm) in V_1, V_2, or V_3, or ≥100μV (1mm) in any other lead] on each SAH Day (n is different for each SAH Day - see Figure 15).

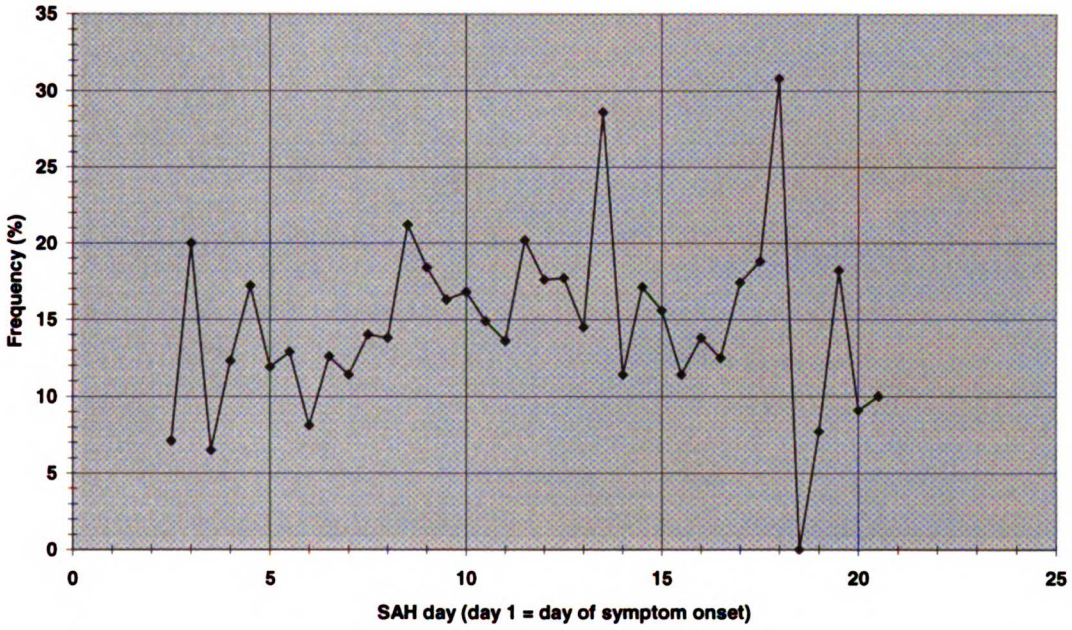

Figure 18. Frequency (%) of ST segment depression measured at the J point [≥100μV (1mm) in any lead] on each SAH Day (n is different for each SAH Day - see Figure 15).

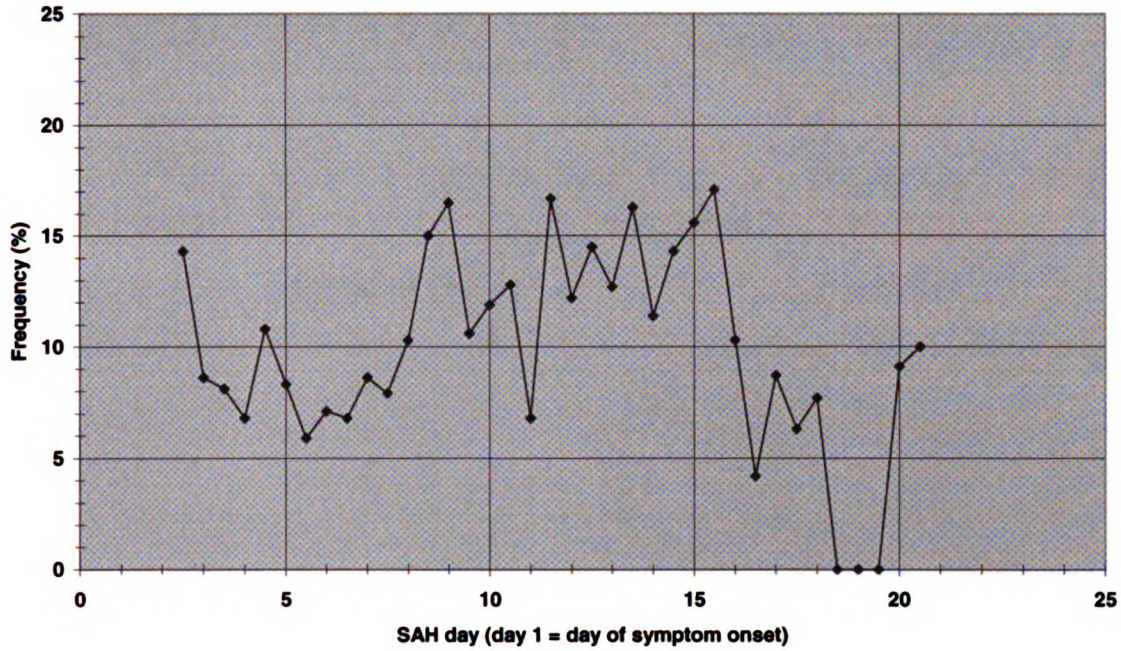

Figure 19. Frequency (%) of ST segment depression measured at 60ms after the J point [≥100μV (1mm) in any lead] on each SAH Day (n is different for each SAH Day - see Figure 15).

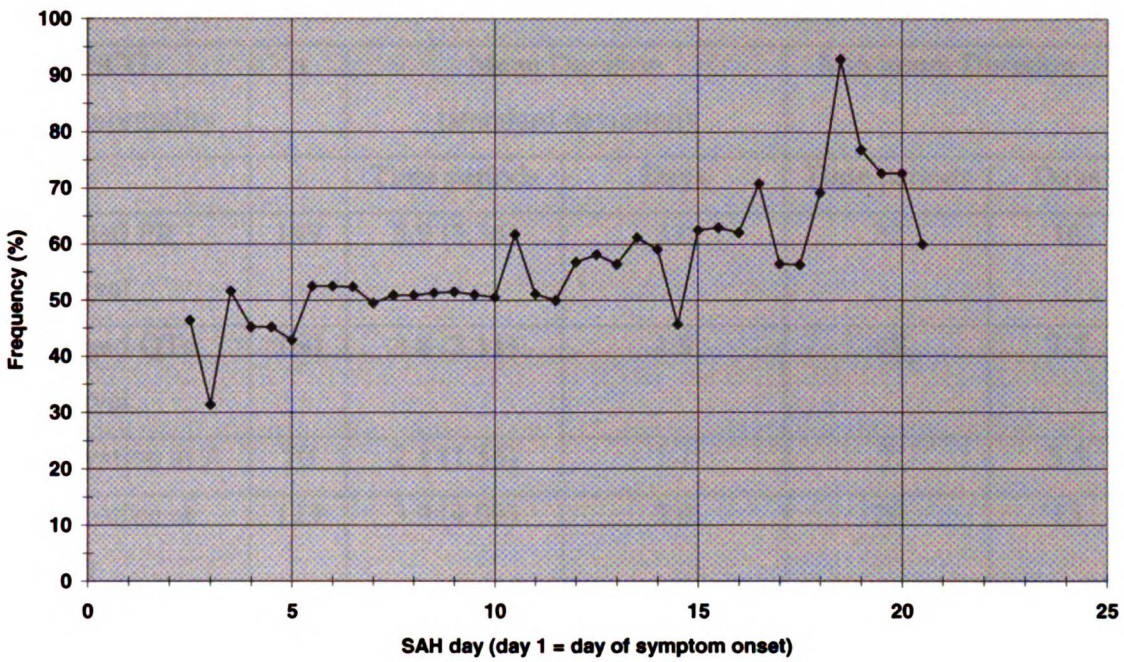

Figure 20. Frequency (%) of T wave inversion [≥100μV (1mm) in any lead] on each SAH Day (n is different for each SAH Day - see Figure 15).

Table 17
Mean and Maximum Duration of ECG Abnormalities After Subarachnoid Hemorrhage in Number of Consecutive Time Periods and Days of Duration

ECG Abnormality	n	Mean Duration (standard deviation)		Maximum Duration	
		Time periods	Days	Time periods	Days
Shortened PR interval	149	5.9 (5.34)	3.0	32	16
Prolonged QTc interval	160	3.8 (3.11)	1.9	15	7.5
ST elevation at J	70	2.1 (1.55)	1.1	7	3.5
ST elevation at J+60	113	3.9 (4.09)	2.0	26	13
ST depression at J	86	2.4 (2.31)	1.2	16	8
ST depression at J+60	76	2.1 (2.23)	1.0	16	8
T wave inversion	160	5.5 (5.13)	2.8	26	13
U wave elevation	45	-	2.7 (2.56)	-	11
T2 deflection	22	-	1.9 (1.9)	-	5

Discussion

Timing of ECG Abnormalities in the Clinical Course

This study is the first to use continuous 12-lead ECG monitoring to determine the timing of ECG abnormalities in the clinical course of SAH and the length of time that these abnormalities persist after the onset of SAH symptoms.

There are very few data from past studies on time of occurrence of ECG changes in relation to the onset of SAH. Di Pasquale et al. (1987) found that 90% of patients with

SAH had ECG abnormalities in the first 48 hours, and concluded that there was a higher rate of occurrence earlier in the course of illness. However, they collected data primarily in the first few days after SAH and relied on a single 12-lead tracing per patient recorded on admission followed by a 24 hour Holter tracing. It is possible that the Holter monitoring, which reflected only two ECG leads, may have missed abnormalities that occurred in unrecorded leads in the days after the SAH event.

In a 12-lead ECG investigation, Brouwers et al. (1989) found that the most pronounced ECG changes were demonstrated during the first 72 hours after SAH. Their study included 61 patients, 26 of whom had daily ECGs and 43 patients who had an ECG recorded three times weekly, both for a period of 12 days or until surgery or death.

Our study, which spanned approximately 20 days of monitoring after onset of SAH symptoms, revealed patterns of occurrence that are somewhat unexpected. While abnormal shortening of the PR interval occurred at some level on all days studied, the frequency rate did not peak until day 12, which is further into the clinical course than included by most other studies. Frequency of prolonged QTC interval was high throughout the 20 days studied, but it also peaked late in the course, at day 16.5. Other ECG abnormalities with higher incidence of occurrence late in the 20 day period included ST segment elevation measured both at the J point and at J+60, ST segment depression measured at the J point, and T wave inversion. Only ST depression at J+60, abnormal U waves, and T2 deflections showed a general pattern of declining frequency toward later days in the clinical course.

These patterns of increased frequency later in the course of illness may be explained by the possible presence of a higher level of disease severity or complications

in patients who remain in the intensive care unit many days after the SAH event. ECG abnormalities after SAH have been theorized to be the result of excessive sympathetic stimulation that causes local catecholamine release from the intracardiac sympathetic nerves and subsequent myocardial injury. If rebleeding or neurological insult occur later in the course of illness, it is possible that this might cause continuing cardiac effects. Further study is needed to investigate how clinical factors, including disease severity and therapeutic interventions, may affect the timing and duration of ECG abnormalities after SAH.

Duration of ECG Abnormalities

Duration of ECG changes after SAH has not been reported extensively in the past. No study to date has obtained continuous 12-lead ECGs on patients with SAH, and those looking at serial tracings recorded on a systematic basis are few. Unfortunately, even some studies that included multiple ECGs over time failed to report data on duration of abnormalities (Brouwers et al., 1989; Cruickshank, Neil-Dwyer, & Brice, 1974; Kreus, Kemilä, & Takala, 1969, Salvati et al., 1992; Umali, Gould, & Gomprecht, 1971).

In one of the earliest studies, ECG abnormalities were reported to persist for 9 to 11 days after stroke among 17 patients, but the type of stroke was not reported (Burch, Meyers, & Abildskov, 1954). Hunt, McRae, & Zapf (1969), in a study of 12 patients, found that ECG abnormalities present on admission returned to normal within seven to eleven days in most patients, while they persisted in one patient for 11 days.

Eisalo, Peräsalo, & Halonen (1972) reported on 20 patients with ECG abnormalities after SAH. QT interval prolongation present on admission resolved by day three, while U waves lasted for 3 to 13 days. ECGs returned to normal in eight of 12

patients who survived within 14 to 17 days, except for one patient in whom a normal ECG was recorded on day 9. Rudehill, Olsson, Sundqvist, & Gordon (1982) reported that T wave abnormalities became less pronounced or resolved, and prolonged QTc interval normalized by 48 hours after admission. In a recent retrospective study, investigators found that ST elevation normalized within one week in all patients, but T waves changes persisted for up to three months after onset (Kuroiwa, Morita, Tanabe, & Ohta, 1995).

In our current study, we found that mean duration of ECG abnormalities ranged from one day for ST depression measured at J+60, to 3 days for shortened PR interval. The maximum durations, however, ranged widely from 3.5 days for ST elevation measured at the J point, to 16 days for shortened PR interval. It should be noted that these are conservative measures of duration. A number of patients had gaps of varying length in ECG recordings when monitoring was suspended during surgery or interventional procedures. ECG abnormalities were not considered to occur continuously if there was no ECG recorded during any one 12 hour time period. Thus, the abnormality may have persisted during the gap in monitoring, but continuity of duration was considered to end with the beginning of that gap in the data.

Limitations of the Study

Since 89% of patients in this sample were transferred from other institutions, the majority were enrolled into this study no earlier than SAH Day 2 or 3. This resulted in insufficient data to evaluate either timing or duration of ECG abnormalities for the 24-hour period immediately following SAH. This may have influenced the patterns of occurrence for some of the ECG abnormalities studied.

We studied patients only during their intensive care unit stay. Most ECG abnormalities were still present at the end of the monitoring period, and it is unknown how long these changes persisted into the recuperative phase. Further study is needed to determine if and when ECG abnormalities resolve after discharge from intensive care.

Conclusions

Most abnormalities included in the study occurred in some proportion of patients on all days studied after SAH (SAH Day 2 to Day 20). Frequency of occurrence of shortened PR interval, prolonged QTc interval, ST segment elevation measured both at the J point and J+60, ST segment depression measured at the J point, and T wave inversion all had peaks in occurrence later than SAH Day 12. Only ST depression measured at J+60, abnormal U waves, and T2 deflections showed a general pattern of declining frequency toward later days in the clinical course.

Mean duration of ECG abnormalities ranged from one day for ST depression measured at J+60, to three days for shortened PR interval. Maximum durations of abnormalities ranged widely from 3.5 days for ST elevation measured at the J point, to 16 days for shortened PR interval.

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Chapter 7: Summary and Conclusions

SAH is a serious neurological disorder that is frequently complicated by the occurrence of ECG abnormalities unexplained by pre-existing cardiac condition. These abnormalities include changes in the morphology of waveforms and duration of intervals, particularly those reflecting myocardial repolarization, on the 12-lead ECG. This phenomenon was first reported more than 50 years ago, but its incidence, characteristics, and prognostic significance have not yet been fully explored. The etiology of these ECG changes remains unproven, and much remains to be learned about the relationship of these abnormalities to other cardiac responses in the setting of SAH, including myocardial wall motion abnormalities, cardiac histological changes, serum cardiac enzyme elevation, and neurogenic pulmonary edema.

The goal of this proposed dissertation research was to determine the prevalence, temporal characteristics, and clinical significance of electrocardiographic abnormalities that occur during the acute phase of aneurysmal SAH. While there have been several previous investigations of this phenomenon, this study was be the first to utilize continuous 12-lead ECG monitoring, as well as computerized ECG measurements.

The pilot analysis of initial ECGs in patients with SAH guided the selection of ECG variables for the later prevalence study by determining which ECG abnormalities occurred most commonly on admission ECGs. Repolarization abnormalities were found to be present in a high proportion of patients, as was QRS voltage suggestive of LVH, but unrelated to hypertension or coronary artery disease. Prolonged QTc after SAH was found to be significantly related to myocardial injury, but not related to mortality, and there was no association between ST-T wave abnormalities and either myocardial injury

or mortality.

The subsequent comparison of the initial ECGs of patients with SAH with normal adult patients further clarified and broadened understanding of the many ECG differences in patients with SAH. Of particular interest are those affecting QRS complex amplitude, ST segment amplitude, and T wave direction and morphology. Several ECG variables were added to the study of prevalence as a result of these findings.

The next step in the progression of this research was the study of the prevalence of selected ECG abnormalities. In this investigation, continuous 12-lead ECG data was collected during a three year period, and a total of 89,430 ECGs collected on 227 patients was included in the analysis. ECG abnormalities occurred in 98% of patients with SAH during the intensive care stay. QRS amplitude abnormalities suggestive of LVH were found in most patients, but were largely transient.

Relationships were explored between demographic, risk factor, disease severity, and outcomes measures. A history of smoking was predictive of occurrence of shortened PR interval and history of hypertension was predictive of occurrence of ST depression and T wave inversion. Disease severity was found to be a strong independent predictor of prolongation of the QTc interval. Prolonged QTc was significantly related to myocardial injury, and T wave inversion was highly predictive of myocardial dysfunction. ECG abnormalities were not found to be predictive of all-cause in-hospital mortality among patients with SAH.

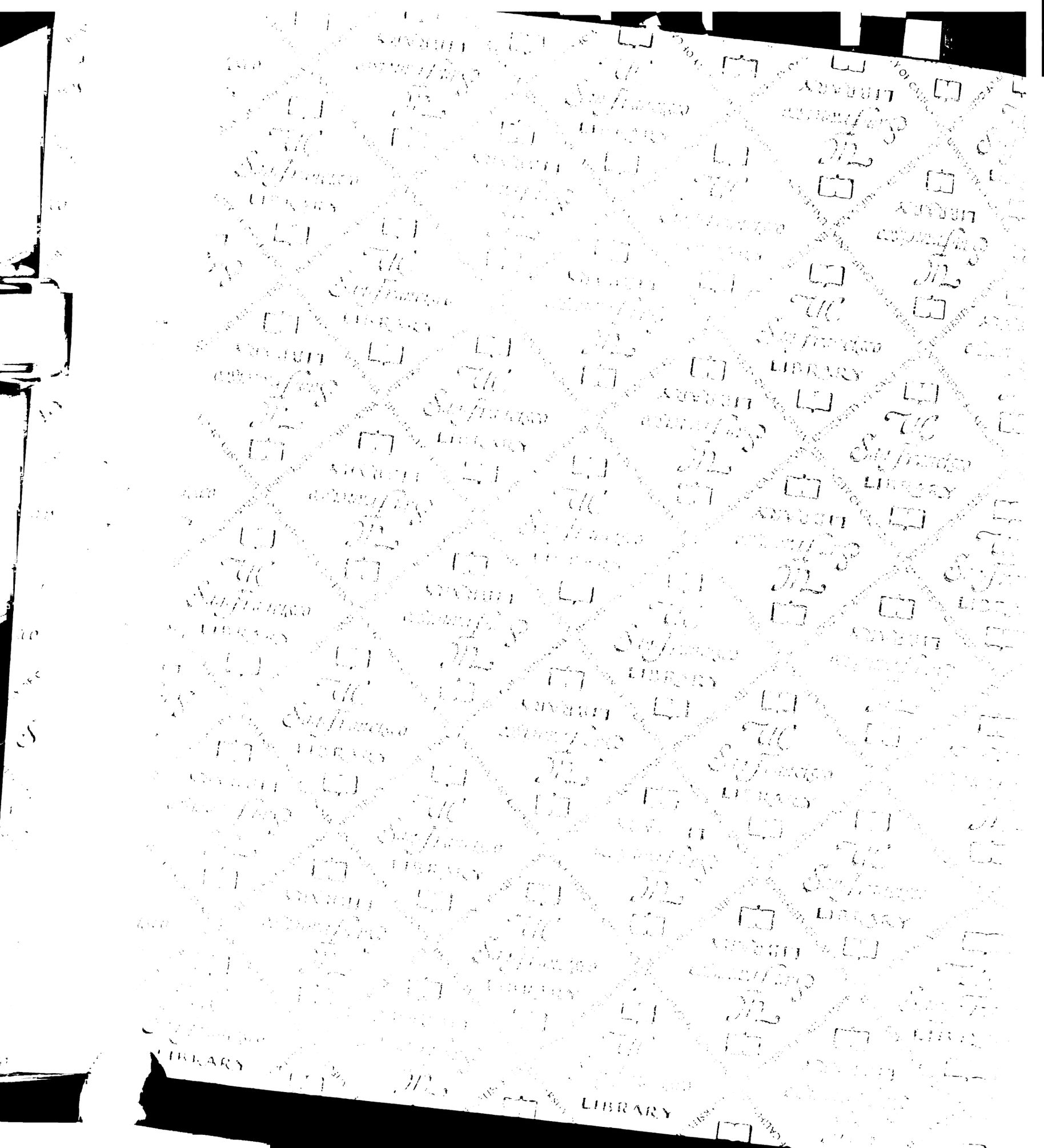
Finally, analyses were performed to clarify the timing of ECG abnormalities in the clinical course of SAH. Most abnormalities included in the study occurred in some proportion of patients on all days studied after SAH (SAH Day 2 to Day 20). Shortened

PR interval, prolonged QTc interval, ST segment elevation measured both at the J point and J+60, ST segment depression measured at the J point, and T wave inversion all in occurred most frequently later than SAH Day 12. Only ST depression measured at J+60, abnormal U waves, and T2 deflections showed a general pattern of early peak occurrence, then declining frequency toward later days in the clinical course.

Mean duration of ECG abnormalities ranged from one day to three days, while maximum durations of abnormalities ranged widely from 3.5 days for ST elevation measured at the J point, to 16 days for shortened PR interval.

Continuous 12-lead ECG monitoring resulted in data collection that was more comprehensive than that in any previous studies of ECG abnormalities in SAH. This dissertation research has stimulated new questions that should be the focus of future study. The transient nature of ECG abnormalities suggestive of LVH should lead to a study of the accuracy of standard ECG criteria for LVH in the SAH population. Peaking of occurrence of most ECG abnormalities late in the clinical course seems to suggest that there may be some relationship between clinical variables, such as disease severity, complications, or interventional procedures, in the occurrence of ECG abnormalities after SAH. Further research comparing ECG data to measures of cardiac function may clarify the relationship between ECG abnormalities and patient outcomes.

Further investigation into the characteristics and prognostic significance of ECG abnormalities in patients with SAH will provide essential information about the underlying neurological and cardiac processes. Previous research on ECG abnormalities in the setting of SAH has just touched the surface, and a great deal needs to be learned in order to manage these patients optimally.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