

# Prolongation of the Corrected QT Complex – A Cause of Sudden Cardiac Death in the Mountain Environment?

JS Windsor<sup>1</sup>, GW Rodway<sup>2</sup>, R Mukherjee<sup>1</sup>, PG Firth<sup>3</sup>, M Shattock<sup>4</sup>, HE Montgomery<sup>1</sup>

<sup>1</sup>UCL Centre for Altitude, Space and Extreme Environment Medicine Institute of Human Health and Performance, University College London, Charterhouse Building, Archway Campus, Highgate Hill, London; <sup>2</sup>College of Nursing and School of Medicine, University of Utah, Salt Lake City, Utah, USA; <sup>3</sup>Department of Anesthesia and Critical Care, Massachusetts General Hospital, Boston, Massachusetts, USA; <sup>4</sup>Cardiovascular Division, The Rayne Institute, 4th Floor, Lambeth Wing, St Thomas' Hospital, London

## Abstract

In the mountain environment sudden cardiac death (SCD) has been shown to be responsible for the deaths of up to 52% of downhill skiers and 30% of hikers. The majority of SCD's are precipitated by a ventricular arrhythmia. Although most are likely to result from structural abnormalities associated with conditions such as ischaemic heart disease, a small but significant number may be due to abnormalities in ion channel activity, commonly known as, "channelopathies". Channelopathies have the potential to lengthen the time between ventricular depolarisation and repolarisation that can result in prolongation of the corrected QT interval (QTc) and episodes of polymorphic ventricular tachycardia (PVT) and eventually, ventricular fibrillation. This review examines the factors that prolong the QTc interval in the mountain environment and outlines a practical framework for preventing the life threatening arrhythmias that are associated with this condition.

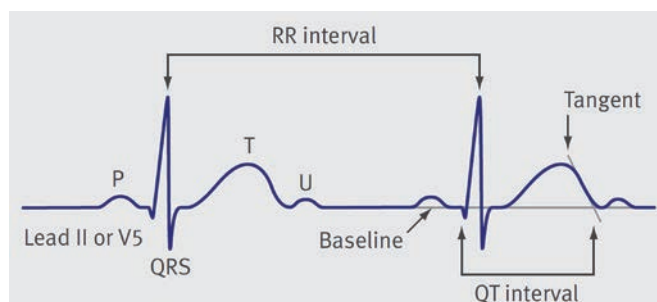
## Introduction

"Sudden death in an otherwise healthy young person is an emotionally devastating event and unfortunately an all-too-common presentation of genetic arrhythmia syndrome" [1].

Sudden Cardiac Death (SCD) can be defined as, "unexpected natural death from a cardiac cause within a short time period, generally <1 hour from the onset of symptoms, in a person without any prior condition that would appear fatal" [2]. SCD is the most common fatal manifestation of cardiac disease, accounting for 456,076 out of 719,456 (63.3%) deaths caused by cardiac disease each year in the USA [2]. In the mountain environment SCD has been shown to be responsible for the deaths of up to 52% of downhill skiers and 30% of hikers [3,4]. The incidence of SCD during these activities is significantly greater than that found in the general population [5]. Amongst men aged over 34 years, the risk of SCD is increased by a factor of 4.3 during mountain hiking and 2.1 during downhill skiing [5]. The majority of SCD's in these cases are precipitated by a ventricular arrhythmia [6]. Although most are likely to result from structural abnormalities associated with conditions such as ischaemic heart disease, a small but significant number are due to abnormalities in ion channel activity. These conditions are commonly known as, "channelopathies" and in some cases are known to lengthen the time between ventricular depolarisation and repolarisation. This delay prolongs the corrected QT interval (QTc) and increases the risk of developing of polymorphic ventricular tachycardia (PVT) and ventricular

fibrillation (Figures 1 & 2) [1,7]. Although episodes of PVT are often short lived, several runs can occur in rapid succession and cause dizziness, syncope, palpitations, seizures and even cardiac arrest [8,9]. Recently, a study of 1866 deaths amongst young competitive athletes in the USA revealed that QTc prolongation was responsible for approximately 2% of fatalities [10]. In adults the phenomenon is thought to contribute to more than 5000 deaths in the USA each year [11].

In this review we shall examine the factors that prolong the QTc interval in the mountain environment and outline a practical framework for preventing the life threatening arrhythmias that are associated with this condition.



**Figure 1:** The QT interval is measured from the onset of the Q wave to the end of the T wave. This point is often defined as the intersection of the tangent to the steepest downslope of the T wave and the baseline. To calculate the corrected QT (QTc) for a given heart rate, the QT interval is divided by the square root of the RR interval ( $QTc = QT / \sqrt{RR}$ ) [Bazett's Formula].

Corresponding Author: Dr J S Windsor, UCL Centre for Altitude, Space and Extreme Environment Medicine, Institute of Human Health and Performance, University College London, Charterhouse Building, Archway Campus, Highgate Hill, London N19 5LW  
Tel: 00 44 207 288 3890 Fax: 00 44 207 288 3892

The QTc is measured in Lead II and is considered normal if it is less than 440 in men and 460 in women [8].



Figure 2: An episode of Polymorphic Ventricular Tachycardia (PVT) in Lead II [12].

### The Causes of QTc Interval Prolongation

Traditionally, the causes of QTc prolongation have fallen into two categories – congenital and acquired:

#### Congenital Causes of QTc Prolongation

In the spring of 1957 two Norwegian physicians described SCD's in three siblings who shared a common history of congenital deafness, repeated syncopal attacks and QTc prolongation [7,8]. This condition, subsequently called the Jervell and Lange-Nielsen Syndrome, was found to result from two abnormal KCNQ1 genes on chromosome 11 that subsequently caused abnormalities in the potassium channels of cardiac myocytes and a delay in electrical conduction.

In recent years more than five hundred mutations on twelve different genes have been associated with Long QT Syndrome (LQTS) [13]. The vast majority of these mutations transcribe ion channel proteins that influence the passage of potassium or sodium ions through the cell membrane of the cardiac myocyte [14,15]. The three most common causes of LQTS are LQT 1, LQT 2 and LQT3.

In order to identify those at greatest risk of SCD a scoring system for LQTS has been developed (Table 1) [16]. Whilst individuals with a score of one or less are deemed to be low risk, those with a score of four or more are considered to have a high probability of LQTS. This diagnosis is not to be underestimated. Up to 13% of those with LQTS present with cardiac arrest [17]. For those who survive this first episode, mortality rates remain high. Left untreated, 20% of those with LQTS will die within one year and almost 50% within five years of initial presentation [18].

The treatment of LQTS largely depends upon the presence of genetic mutations and the response to medical therapy. Long acting  $\beta$ -blockers such as atenolol are highly effective in the

management of LQTS 1 and 2 [1,19,20] whilst mexiletine, a sodium channel blocker have been shown, albeit in small studies, to shorten the cardiac action potential in LQTS 3 and prevent episodes of PVT [21]. In those who fail to respond to medical treatment, the use of an implantable defibrillator is indicated [22]. If this is not possible, thoracoscopic left cardiac sympathectomy has been shown to be a highly effective alternative [23]. In addition to these interventions, those with LQTS need to be aware of other triggers that prolong the QTc interval and modify their behaviour accordingly.

#### Acquired Causes of QTc Prolongation

The length of the QTc interval can be affected by a wide range of clinical factors. Whilst non-modifiable factors such as increasing age and female gender have been shown to cause QTc prolongation, there are a number of modifiable factors which are amenable to treatment:

##### Cardiovascular Disease (CVD)

A wide range of cardiovascular diseases (CVD) have been associated with the prolongation of the QTc interval (Table 2).

- Myocardial Infarction
- Dilated Cardiomyopathy
- Congestive Cardiac Failure
- Hypertrophic Cardiomyopathy
- Hypertension
- Complete Heart Block
- Kawasaki's Disease
- Myocarditis

Table 2: Cardiovascular diseases associated with a prolongation of the QTc interval [24].

This increase is thought to be largely due to reduced outward potassium channel function causing the cardiac action potential to lengthen and therefore trigger runs of PVT [25].

In the mountain environment the fall in the partial pressure of inspired oxygen ( $P_{iO_2}$ ) results in profound changes in the systemic and pulmonary circulation. These changes, covered

| Electrocardiographic Changes <sup>†</sup> |     | Clinical History                  |
|---|-----|-----------------------------------|
| Corrected QT Interval:                    |     | Syncope <sup>‡</sup>              |
| >0.48                                     | 3   | With Stress 2                     |
| 0.46-0.47                                 | 2   | Without Stress 1                  |
| 0.45 (males)                              | 1   | Congenital Deafness 0.5           |
| Torsades De Pointes <sup>‡</sup>          | 2   | <b>Family History<sup>§</sup></b> |
| T Wave Alternans                          | 1   | Family members with LQTS 1        |
| Notched T Wave in 3 Leads                 | 1   | 0.5                               |
| Low Heart Rate for Age                    | 0.5 |                                   |

Table 1: Diagnostic Criteria for LQTS. Redrawn from [16]. Individuals with a score of 1 or less are considered low risk, a score of 2 to 3 is intermediate risk and a score of 4 or more carries a high probability of LQTS. <sup>†</sup>Findings in the absence of medications or disorders known to affect these electrocardiogram findings. The QTc is calculated by Bazett's Formula (Figure 1).<sup>‡</sup>Torsades de pointes and syncope are mutually exclusive. <sup>§</sup>The same family member cannot be counted in both categories. The presence of T wave alternans, notched T waves and a low heart rate are all associated with gene mutations associated with LQTS 1, 2 and 3.

elsewhere in this edition of the Journal, have led to the conclusion that the mountain environment has the potential to, “unmask coronary artery disease, left ventricular dysfunction and pulmonary hypertension that was asymptomatic at sea level” [26].

An increase in sympathetic activity can not only affect those with structural heart disease but also those with LQTS. In normal individuals, sympathetic activity has little or no effect on QTc, however in LQTS, triggers such as exercise and emotional stress are common precipitants of cardiac arrhythmias [27]. Following administration of adrenaline (0.1µg/kg bolus followed by 0.1µg/kg/min infusion) the QTc has been shown to increase by 32% in LQT1 and 24% in LQT2 compared to only 16% in healthy controls (P<0.05) [28]. Sympathetic activity is thought to increase the flow of ions through channels in the myocyte wall that results in an intracellular surplus of positive charge and a delay in ventricular repolarisation [29]. Unfortunately, the effect of the sympathetic stimulus seen at altitude has not been formally assessed in those with LQTS. However, the majority of studies that have looked at the effect of altitude upon healthy individuals have shown that QTc does increase and is sustained throughout an individual's stay at altitude [30-37].

### Drugs

A wide range of drugs can interfere with the movement of potassium and sodium ions within the myocardium leading to prolongation of the QTc interval, episodes of PVT and SCD [24]. In recent years this has led to the well publicised withdrawal of drugs such as terfenadine, droperidol and cisapride [12]. Some of those who ascend to altitude may receive drugs that affect the QTc interval. These include long term anti-psychotics, anti-depressants and anti-arrhythmics, as well as a wide range of drugs that are prescribed for acute illnesses. Bacterial infections are common at altitude [38]. Quinolones, macrolides and tetracyclines are frequently used. Those who develop Acute Mountain Sickness (AMS) may treat their nausea and vomiting with domperidone, whilst victims of High Altitude Pulmonary Edema (HAPE) tend to use nifedipine to either treat or prevent their condition [39]. Long acting beta-2 agonists such as salmeterol are also used in the prevention of HAPE. Whilst their effect upon the QTc interval is unclear, there is evidence to suggest that in a hypoxic environment prolongation may occur [40].

### Electrolyte Disturbances

Prolongation of the QTc interval has been linked to low concentrations of serum electrolytes such as calcium, magnesium and potassium [24]. Changes in the intake and output of these electrolytes can vary significantly in the mountain environment. Episodes of gastroenteritis are common and can cause prolonged episodes of vomiting and diarrhoea that lead to significant losses of fluid and electrolytes. This can be compounded by a reduction in intake. Episodes of Acute Mountain Sickness (AMS) and High Altitude Cerebral Edema (HACE) can cause lethargy and nausea, whilst bouts of tonsillitis and pharyngitis can make swallowing uncomfortable. The effect of these disturbances upon the QTc interval may be compounded by the concomitant use of diuretics, since some degree of electrolyte imbalance may already be present. Despite a paucity of evidence and the concerns of a number of high altitude physicians, diuretics are still commonly used for the treatment of life threatening illnesses such as HAPE and HACE [41].

Acclimatisation to altitude is associated with hyperventilation and an increase in pH has the potential to reduce the concentrations of ionised electrolytes in the cardiac myocyte and therefore interfere with normal cellular function.

### Weight Loss

Factors such as low weight, low body mass index and rapid weight loss have all been shown to be associated with QTc prolongation [42]. In the mountain environment weight loss is common and results from a combination of reduced intake, increased energy expenditure and in some cases, changes in absorption [43,44]. Typically, weight loss is greatest above 5000m [45]. During the 1981 American Medical Research Expedition to Mt Everest (AMREE) thirteen members lost on average 1.9kgs during a 23 day trek to Mt Everest Base Camp (5300m). However higher on the mountain this increased by a further 4kgs (range 0-8kg) over the course of 26 days [46]. In some cases weight loss can be dramatic. Anecdotal reports of 10 to 20 kgs weight loss on Mt Everest (8850m) are not unusual. Clearly, this degree of weight loss is comparable to those with eating disorders and may therefore be associated with prolongation of the QTc interval.

### Hypothermia

A fall in core temperature below 35°C can quickly result in bradycardia, heart block and prolongation of the PR, QRS and QT intervals [47]. A recent case series of four patients who underwent therapeutic hypothermia (35°C) following cardiac arrest found that all developed QTc prolongation (>460ms) during cold exposure and only improved once warming had been commenced [48].

### Other Conditions

A number of other common medical conditions are associated with prolongation of the QTc interval. These include: head injury, hypothyroidism, diabetes mellitus, obesity and hepatic impairment.

## A Practical Framework for Preventing QTc Prolongation and its Complications in the Mountain Environment.

In order to prevent complications of QTc prolongation in the mountain environment it is vital to first identify those at greatest risk and provide these individuals with appropriate treatment. Children and young adults who experience episodes of dizziness, syncope, palpitations and seizures should be screened for congenital LQTS [49]. Once a clinical diagnosis has been established, further genetic testing may then be useful to determine prognosis and appropriate medical treatment [1,20]. At present, it is unclear how those with congenital LQTS cope at altitude. However given the factors that can prolong the QTc interval at altitude, the authors of this article recommend that those with congenital LQTS should remain below 2500m. Making a single recommendation for those at risk of acquired LQTS is impossible since a much wider spectrum of risk is present. Provided that underlying medical conditions are well controlled and other modifiable risk factors are managed, a safe and successful ascent to altitude should be possible. However there will be individuals with acquired LQTS who have a similar degree of risk as those with the congenital form of the syndrome. These individuals should be advised to stay below 2500m.

In the event of a suspected episode of PVT at altitude, Table 3 lists the steps that should be taken:

Lie patient down in supine position  
 Keep patient warm and comfortable  
 Administer supplemental oxygen (2-4 l/min)  
 Encourage patient to eat and drink  
 Omit drugs that may prolong the QTc interval  
 Optimise chronic medical conditions  
 (eg diabetes mellitus, hypertension, hypothyroidism, pain)  
 Treat precipitating medical conditions  
 (eg HAPE, gastroenteritis)  
 Provide reassurance and support  
 Arrange urgent evacuation

**Table 3: Treatment for those with suspected PVT**

In a hospital environment further medical treatment may consist of:

Magnesium Sulphate – 2g IV bolus over 2-3 minutes followed by an IV infusion at a rate of 2-4mg per minute. An additional 2g bolus can be given in the event of a further episode of PVT [50].

Potassium Chloride – Appropriate slow IV boluses should be administered in order to maintain a normal or high normal (4.5-5.0mEq/L) potassium plasma concentration [49].

Temporary Transvenous Cardiac Pacing – If electrolyte replacement does not prevent PVT a temporary transvenous pacing wire should be inserted and set to pace at 90-110 beats per minute [51].

An ascent to altitude can coincide with an increase in the QTc interval. In those with LQTS this has the potential to trigger episodes of PVT and SCD. Preventing the consequences of this condition needs not only an approach that identifies the risk factors for QTc prolongation, but also recognises the symptoms of LQTS and implements a practical plan of management in the field. Symptoms such as dizziness, syncope, palpitations and seizures in the mountain environment should raise the possibility of LQTS and trigger an appropriate response from physicians.

## References

- Roden DM. Long QT syndrome *N Eng J Med* 2008; 358: 169-176
- Zheng ZJ, Croft JB, Giles WH et al. Sudden Cardiac Death in the United States, 1989 to 1998. *Circulation* 2001; 104: 2158-2163
- Sherry E, Clout L. Deaths associated with skiing in Australia: a 32 year study of cases from the Snowy Mountains. *Med J Aust* 1988; 149: 615-8
- Burtscher M, Philadelphia M, Likar R. Sudden cardiac death during mountain hiking and downhill skiing. *N Eng J Med* 1993; 329: 1738-9
- Windsor JS, Van Der Kaaij J, Rodway GW, Mukherjee R, Montgomery HE. Sudden cardiac death in the mountain environment. *Med Sportiva* 2009; 13(3): 146-151
- Albert CM, Mittleman MA, Chae CU et al. Triggering of sudden death from cardiac causes by vigorous exertion. *New Eng J Med* 2000; 343: 1355-61
- Morita H, Wu J, Zipes DP. The QT syndromes: long and short. *Lancet* 2008; 372: 750-763
- Abrams DJ, Perkin MA, Skinner JR. Long QT syndrome. *Brit Med J* 2010; 340: 314-316
- MacCormick JM, McAlister H, Crawford J et al. Misdiagnosis of long QT syndrome as epilepsy at first presentation. *Ann Emerg Med* 2009; 54: 26-32
- Maron BJ, Doerer JJ, Haas TS et al. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980-2006. *Circulation* 2009; 119: 1085-1092
- Vincent G. The molecular genetics of the long QT syndrome: genes causing fainting and sudden death. *Ann Rev Med* 1998; 49: 263-274
- Gupta A, Lawrence AT, Krishnan K et al. Current concepts in the mechanisms and management of drug-induced QT prolongation and torsade de pointes. *Am Heart J* 2007; 153: 891-899
- Goldenberg I, Bradley J, Moss A et al. Beta-blocker efficacy in high risk patients with the congenital long QT syndrome types 1 and 2: implications for patient management. *J Card Electrophysiol* 2010; 21(8): 893-901
- Goldenberg I, Moss AJ. Long QT syndrome. *J Am Coll Cardiol* 2008; 51: 2291-2300
- Webster G, Berul CI. Congenital Long QT syndromes: a clinical and genetic update from infancy through adulthood. *Trends Cardiovasc Med* 2008;18:216-224
- Schwartz PJ, Moss AJ, Vincent GM et al. Diagnostic criteria for the long QT syndrome: an update. *Circulation* 1993; 88: 782-784
- Priori SG, Schwartz PJ, Napolitano C et al. Risk stratification in the long QT syndrome. *N Engl J Med* 2003; 348: 1866-1874
- Schwartz PJ. Idiopathic long QT syndrome: progress and questions. *Am Heart J* 1985; 109: 399-411
- Morita H, Wu J, Zipes DP. The QT syndromes: long and short. *Lancet* 2008; 372: 750-763
- Moss AJ. Long QT syndrome. *JAMA* 2003; 289(16): 2041-2044
- Schwartz PJ, Priori SG, Locati EH et al. Long QT syndrome patients with mutations of the SCN5A and HERG genes have differential responses to Na channel blockade and to increases in heart rate: implications for gene specific therapy. *Circulation* 1995; 92: 3381-3386
- Daubert JP, Zareba W, Rosero SZ et al. Role of implantable cardioverter defibrillator therapy in patients with long QT syndrome. *Am Heart J* 2007; 153: 53-58
- Schwartz PJ, Priori SG, Cerrone M et al. Left cardiac sympathetic denervation in the management of high risk patients affected by the long QT syndrome. *Circulation* 2004; 109: 1826-1833
- Camm AJ, Malik M, Yap YG. *Acquired long QT syndrome* Oxford: Blackwell, 2004.
- Browne KE, Prystowsky E, Heger JJ et al. Prolongation of the QT interval in man during sleep. *Am J Cardiol* 1983; 52(1): 55-59
- Bartsch P, Gibbs SR. Effect of altitude on the heart and lungs. *Circulation* 2007; 116: 2191-2202
- Wilde AA, Jongbloed RJ, Doevendans PA et al. Auditory stimuli as a trigger for arrhythmic events differentiate HERG-related (LQT2) patients from KVLQT1-related patients (LQT1). *J Am Coll Cardiol* 1999; 33: 327-332
- Noda T, Takaki H, Kurita T et al. Gene specific response to dynamic ventricular repolarization to sympathetic stimulation in LQT1, LQT2 and LQT3 forms of congenital long QT syndrome. *Eur Heart J* 2002; 23: 975-983
- Shimizu W, Antzelevitch C. Differential response to beta adrenergic agonists and antagonists in LQT1, LQT2 and LQT3 models of the long QT syndrome. *J Am Coll Cardiol* 2000; 35: 778-786
- Albrecht H, Albrecht E. Ergometric, rheographic, reflexographic and electrocardiographic tests at altitude and effect of drugs on human physical performance. *Fed Proc* 1969; 28(3): 1262-1267
- Alexander JK. Age, altitude and arrhythmia. *Tex Heart Inst J* 1995; 22: 308-316

32. Das BK, Tewaru SC, Parashar SK et al. Electrocardiographic changes at high altitude. *Ind Heart J* 1983; 35(1): 30-33
33. Horii M, Takasaki I, Ohtsuka K et al. Changes of heart rate and QT interval at high altitude in alpinists: analysis by holter ambulatory electrocardiogram. *Clin Cardiol* 1987; 10: 238-242
34. Penalzoa D, Echevarria M. Electrocardiographic observations on ten subjects at sea level and during one year of residence at high altitudes. *Am Heart J* 1957; 54(6): 811-822
35. Politte LL, Almond CH, Logue JT. Dynamic electrocardiography with strenuous exertion at high altitudes. *Am Heart J* 1968; 75: 570-572
36. Sanders JS, Martt JM. Dynamic electrocardiography at high altitude. *Arch Intern Med* 1966; 118: 132-138
37. Shi Z, Ning X, Zhu S et al. Electrocardiogram made on ascending the Mount Qomolangma from 50 asl. *Sci Sin* 1980; 23(10): 1316-1325
38. Rodway GW, Windsor JS. Airway mucociliary function at high altitude. *Wild Env Med* 2006; 17(4): 271-2755
39. Luks AM, McIntosh SM, Grissom CK et al. Wilderness Medical Society consensus guidelines for the prevention and treatment of acute altitude illness. *Wilderness Environ Med* 2010; 21(2): 146-155
40. Bremner P, Burgess CD, Crane J et al. Cardiovascular effects of fenoterol under conditions of hypoxaemia. *Thorax* 1992; 47: 814-817
41. Luks AM. Do we have a "best practice" for treating high altitude pulmonary edema? *High Alt Med Biol* 2008; 9(3): 111-114
42. Swenne I, Larsson PT. Heart risk associated with weight loss in anorexia nervosa and eating disorders: risk factors for QTc interval prolongation and dispersal. *Acta Paediatr* 1999; 88: 304-309
43. Hultgren H. *High altitude medicine*. Stanford: Hultgren Publications, 1998
44. Brooks GA, Butterfield GE. Metabolic responses of lowlanders to high altitude exposure. In: Hornbein TF, Schoene RB (eds) *High altitude: an exploration of human adaptation* New York: Marcel Dekker, 2001; Ch 17
45. Ward MP, Milledge JS, West JB. High altitude medicine and physiology. 3rd Edn. London: Arnold, London, 2000.
46. Boyer SJ, Blume FD. Weight loss and changes in body composition at high altitude. *J Appl Physiol* 1984; 57: 1580-1585
47. Mattu A, Brady WJ, Perron AD. Electrocardiographic manifestations of hypothermia. *Am J Emerg Med* 2002; 20(4): 314-326
48. Khan JN, Prasad N, Glancy JM. QTc prolongation during therapeutic hypothermia: are we giving it the attention it deserves? *Europace* 2010; 12(2): 266-270
49. Khan IA. Clinical and therapeutic aspects of congenital and acquired long QT syndrome. *Am J Med* 2002; 112: 58-66
50. Tzivoni D, Banai S, Schuger C et al. Treatment of torsade de pointes with magnesium sulphate. *Circulation* 1988; 77: 392-397
51. Di Segni E, Klein HO, David D et al. Overdrive pacing in quinidine syncope and other long QT interval syndromes. *Arch Intern Med* 1980; 140: 1036-1040