FACULDADE DE MEDICINA DA UNIVERSIDADE DE COIMBRA

TRABALHO FINAL DO 6º ANO MÉDICO COM VISTA À ATRIBUIÇÃO DO GRAU DE MESTRE NO ÂMBITO DO CICLO DE ESTUDOS DE MESTRADO INTEGRADO EM MEDICINA

DAVID MANUEL MARQUES PINTO TONELO

HOLIDAY HEART SYNDROME REVISITED AFTER 34 YEARS

ARTIGO DE REVISÃO

ÁREA CIENTÍFICA DE CARDIOLOGIA

TRABALHO REALIZADO SOB A ORIENTAÇÃO DE:
RUI ANDRÉ QUADROS BEBIANO DA PROVIDÊNCIA E COSTA

SETEMBRO 2012
Holiday Heart Syndrome revisited after 34 years

David Tonelo BSc*, Rui Providência MD MSc, Lino Gonçalves MD PhD FESC

Faculty of Medicine, University of Coimbra, Portugal

Abstract

Cardiovascular effects of ethanol have been known for a long time. However most research has focused on beneficial effects (the “French-Paradox”) when consumed moderately or its harmful consequences, such as dilated cardiomyopathy, when heavily consumed for a long time. An association between acute alcohol ingestion and onset of cardiac arrhythmias was first reported in early 70’s. In 1978 Phill Ettinger described for the first time “Holiday Heart Syndrome” as the occurrence, in healthy people without heart disease known to cause arrhythmia, of an acute cardiac rhythm disturbance, most frequently atrial fibrillation, after binge drinking. This name derived from the fact episodes were initially observed more frequently after weekends or public holidays. Thirty-four years have passed since original description of “Holiday Heart Syndrome”, with new research in this field, increasing the knowledge about this entity. Throughout this paper the authors will comprehensively review most of the available data concerning the “Holiday Heart Syndrome” and highlight the currently unsolved questions.

Keywords: Holiday Heart Syndrome; Alcohol; Cardiac arrhythmia

*Corresponding author: Tel: +351 918820405; E-mail address: dvdtonelo@hotmail.com (D.Tonelo)
Introduction

Alcohol is one of the oldest known drugs and it’s the most used recreational drug in the United States of America\textsuperscript{1} and probably in the rest of the globe. Ethanol can have health benefits when consumed moderately, as it seems to offer some degree of cardiovascular protection due to various mechanisms: activation of fibrinolytic system, lower platelet aggregation, antioxidant effect, lipid profile improvement, improved endothelial function and other mechanisms. This cardioprotective effect is known as the “French-Paradox”.\textsuperscript{2} However it is known that ethanol abuse can lead to several diseases in humans, such as the well known alcohol addiction, alcoholic liver disease, dilated alcoholic cardiomyopathy and even cancer such as in oral cavity and esophagus.\textsuperscript{3}

Among the cardiovascular effects, regular alcohol abuse seems to increase blood pressure, leading to arterial hypertension, which by itself is already a risk factor for other cardiovascular diseases\textsuperscript{4} and for sudden death.\textsuperscript{5} It’s also associated with procoagulant changes after acute ingestion, hypocoagulation with chronic abuse and thrombocytosis after withdrawal. Additionally it can also reduce regional cerebral blood flow by affecting cerebral metabolism due to chronic abuse or lead to vasoconstriction of cerebral arteries with acute intake. All these aforementioned effects can lead to stroke and regular abuse is also associated to intracranial hemorrhage, which can be fatal.\textsuperscript{6}

There is also a higher risk of sudden cardiac death with alcohol abuse, increasing with the ingested amount, regardless of the presence of previous heart events like ischemic heart disease or myocardial infarction.\textsuperscript{5}

Chronic consumption of large amounts of alcohol is also associated with alcoholic cardiomyopathy, a subtype of secondary dilated cardiomyopathy, known to be a cause of not only cardiac failure, but also has been associated with atrial fibrillation and other cardiac arrhythmias.\textsuperscript{7–9}
Alcohol seems to be able to cause cardiac arrhythmias in healthy people either by acute excessive alcohol ingestion, commonly known as “binge drinking”, or by chronic ingestion. Arrhythmias due to binge drinking were described as “Holiday Heart Syndrome” (HHS) and will be further developed in this article. Arrhythmia due to chronic drinking seems to have a significant association with consumption(s) >36g ethanol/day, but it is less clear with light and moderate drinking.\textsuperscript{10,11}

As alcohol consumption and binge drinking are common, it’s important to elucidate HHS among medical community and population, so HHS can be diagnosed more easily and preventive measures be taken. Additionally, since it is already been 34 years since the original description by Ettinger et al and some questions have still been left unanswered, we think it is time to organize ideas and put things into perspective.

**Methods**

An electronic search in PubMed was performed using the following string: “alcohol intake AND (AF OR arrhythmias OR atrial fibrillation OR atrial flutter) OR holiday heart”. The search was performed from January 1960 to September 2012. We obtained 436 articles from this main search. After analyzing each abstract, we identified 10 relevant papers concerning HHS and potential alcohol mechanisms behind its arrhythmogenicity. Papers focusing only on chronic alcohol intake and its effects on cardiac function were not included. We also manually examined the reference lists from these identified articles for more relevant articles, repeating the process again, which resulted in 4 new articles added to our list. Five other articles were added at authors discretion from manual searches on specific subjects related to HHS and/or alcohol mechanisms behind its arrhythmogenic properties (figure 1).
I- HHS: History and definition

The “Holiday Heart Syndrome” was first recognized in early 70’s when Philip Ettinger noticed an association between acute intoxicated patients and cardiac arrhythmias, even though at that time most textbooks did not suggest that ethanol could cause cardiac arrhythmias in apparently healthy non-alcoholic people.

The term was officially introduced in 1978 by Ettinger and colleagues, to describe the occurrence of an acute cardiac rhythm disturbance in apparently healthy people after an episode of heavy drinking, i.e. “binge drinking”. This disturbance disappeared with subsequent abstinence, leaving no residual heart disease. These occurrences had the particularity of being more frequent after weekends or holidays like Christmas or New Year’s Eve, which are known to be associated with increased alcohol ingestion, contributing to its
name. However, in a later study, Koskinen et al have shown that this association between arrhythmias caused by recent alcohol intake and weekends or holidays was not always present.

HHS is mainly associated with supraventricular arrhythmias, with atrial fibrillation (AF) being the most common in this syndrome. However other types can also occur like atrial flutter, paroxysmal atrial tachycardia, isolated ventricular premature beats, among other less frequent kinds of arrhythmia.

HHS can occur in regular and non-regular drinkers. However since all patients in Ettinger’s study consumed alcoholic beverages heavily and on a regular basis, initially HHS was thought to be linked mostly to people with a chronic alcohol consumption background than those without. Nevertheless Ettinger and colleagues also describe the case of a healthy non-regular drinker individual presenting with AF after alcohol consumption, hinting that HHS could also occur in this group of subjects. This was later confirmed by other studies showing similar cases of sudden onset of cardiac arrhythmias after heavy drinking in non-alcoholic healthy people.

It is important to note that patients with HHS are apparently healthy, with no personal or familiar history of palpitations or other suggestive symptoms of structural cardiac anomalies or any clinical evidence of heart disease like cardiomyopathy, cardiac valvular disease and coronary heart disease, or other conditions that could lead to cardiac arrhythmias, like abnormal electrolytes levels or elevated thyroid hormone(s) levels. Laboratorial and other tests are usually normal and after returning to normal sinus rhythm the electrocardiograms (ECG) were mostly normal.

Another particular characteristic of HHS is the lack of new episodes with alcohol abstinence and the recurrence of symptoms with continued alcohol abuse. This observation further strengthens the role of alcohol on developing these arrhythmias and also the
importance of avoiding alcoholic binges, or even not consuming at all, as prevention of new events.\textsuperscript{7,12,13,17}

The most frequent symptom reported by patients with HHS is palpitations. Other symptoms commonly reported are precordial pressure or pain, syncope\textsuperscript{14} and dyspnea.\textsuperscript{7}

However cardiac arrhythmias, like atrial fibrillation, can also occur without any clinical symptoms making HHS harder to be diagnosed, which can underestimate its incidence.\textsuperscript{18}

Atrial fibrillation, the most frequent cardiac arrhythmia in HHS, has been shown to be a major risk factor for stroke\textsuperscript{19} and increased mortality\textsuperscript{20}. This indirectly suggests an association between HHS and stroke or death. Nevertheless, there is no clinical data assessing these outcomes specifically in the setting of HHS. Moreover, arrhythmias associated with HHS after binge drinking can lead to sudden death, which may explain some of the sudden death cases commonly reported in alcoholics.\textsuperscript{5,14}

The key ideas about HHS are summarized in table 1.

\textbf{Table 1 - Key ideas about the Holiday Heart Syndrome}

- HHS is associated with binge drinking, being more frequent after weekend and holidays
- Patients are apparently healthy and have no clinical evidence of cardiac disease
- Can occur in both regular drinkers and non-drinkers
- Atrial fibrillation is the most common arrhythmia associated with HHS
- Palpitations, syncope, precordial pressure or pain and dyspnea are the most common symptoms, however some episodes may be asymptomatic
II- Pathophysiology

The mechanisms behind the association of alcohol and cardiac arrhythmias are still unresolved. These may be direct (ethanol myotoxicity) or indirect (by alcohol derived metabolites or effects in other organs such as adrenal glands). However there are some facts about alcohol arrhythmogenic properties that have been accepted among scientific community (figure 2):

II.I- Cardiac conduction interference: It is thought that acute ethanol ingestion interferes with the cardiac conduction system, through the slowing of conduction. This has an important role since it facilitates re-entry, which is one of main mechanisms underlying the development of cardiac arrhythmias, namely AF.

In an experimental study with dogs, Ettinger et al, did not observe prolongation of neither the HV interval nor QRS widening after acute alcohol infusion. However, these parameters were only measured on 2 dogs. A bigger sample, namely one composed of humans might be necessary to confirm this theory. In fact, later in the original HHS study, prolongation of PRc, QRS and QTc intervals, which are known to be associated with AF, was observed. Cardy and co-workers, have also shown prolongation of P and QRS waves after acute ingestion of ethanol in 13 humans, suggesting atrial and ventricular slowing of conduction due to ethanol. Although controls also had prolongation of these waves, the changes in ethanol group were significantly more pronounced.

A recent study, using the patch clamp technique, has shown that alcohol in a concentration ≥2g/L has an inhibitory effect on cardiac sodium channels, providing a possible mechanism for this cardiac conduction interference caused by acute alcohol ingestion. This may happen directly or even indirectly since the inhibition of sodium channel can increase the activity of sodium-calcium-exchanger, prolonging the action potential and repolarization,
with subsequent prolongation of intervals, such as QT interval, facilitating the onset of cardiac arrhythmias. For concentrations below 2g/L the inhibition wasn’t significant, meaning this mechanism is more likely to occur with acute heavy ingestion (binge drinking).  

**II.II- Shortening of refractory period**: It was shown in rat atrial tissue that alcohol can shorten atrial refractory period, which can lead to cardiac arrhythmias. However, Engel et al, in a study with 11 alcohol abusers did not find significantly alterations in atrial refractory period after whiskey consumption. Therefore there can be additional and significant focal conduction changes that can facilitate re-entry and lead to the cardiac arrhythmias observed in this study.

**II.III- Increased sympathetic activity**: alcohol can increase the release of catecholamines, secreted either by adrenal glands medulla or locally by myocardium itself. This increase of
systemic and intramyocardial catecholamines can lead to the prolongation of P-wave, which is known to be associated with atrial arrhythmias.\textsuperscript{8,9}

However, Mäki and colleagues did not find a significant increase of catecholamine levels after alcohol consumption both in individuals with and without personal history of AF episodes caused by binge drinking. Still, catecholamine levels in the AF group displayed a trend for being higher, which can synergistically work with the other arrhythmogenic mechanisms of alcohol, increasing the likelihood of cardiac arrhythmia. The same authors observed an increase of beta-adrenergic receptors alongside with a predominance of cardiac sympathetic activity, in patients with previous drinking-related AF history.\textsuperscript{26}

II.IV- Raise of plasma free fatty acids: With alcohol intake there is a raise in plasma free fatty acids, which are thought to be arrhythmogenic.\textsuperscript{7,9} Although the mechanisms are still not fully understood, a significant association between elevated free fatty acids and AF was observed in elderly people in a recent analysis of the Cardiovascular Health Study, strengthening this theory.\textsuperscript{27}

II.V- Acetaldehyde: The primary metabolite of alcohol, also seems to exhibit arrhythmogenic properties, possibly by increasing systemic and intramyocardial catecholamines.\textsuperscript{23,26} An experimental study by Gallardo-Carpentier et al, using dogs’ Purkinje fibers, has shown that acetaldehyde has an arrhythmogenic effect, which seems to be caused by an increase in adrenergic activity.\textsuperscript{28} Hence, acetaldehyde could cause the onset of arrhythmias some time after ethanol ingestion. Conversely, arrhythmias have been observed shortly after whisky intake even before significant amounts of acetaldehyde could be produced.\textsuperscript{16}
**Increased parasympathetic activity:** Despite the aforementioned data supporting an increased sympathetic activity after alcohol intake as a cause of cardiac arrhythmias,\textsuperscript{26} a recent study by Mandyam and co-workers identified a connection between vagal activation and Paroxysmal Atrial Fibrillation (PAF). It also suggested that alcohol could trigger AF by vagal activation since patients reporting alcohol as trigger were more likely to report vagal activation as trigger.\textsuperscript{29}

### III- Clinical evidence

Apart from Ettinger’s original description, the link between binge drinking and onset of cardiac arrhythmias has been consistently observed (table 2).

*Engel et al* tested the vulnerability to AF and flutter after whiskey consumption. In this study, 2 out of 3 non-alcoholic patients with sinus bradycardia, but without heart failure, developed atrial fibrillation or flutter after consuming whisky.\textsuperscript{16}

A case series, by Thornton, showed 4 cases of cardiac arrhythmia after alcohol intake in persons without regular alcohol consumption.\textsuperscript{7}

*Koskinen* and colleagues, in a case-control study with 100 patients, including 35 with no evidence of cardiac disease, also verified a link between recent alcohol intake (previous 2 days) and AF. However, unlike the original the HHS study, most of the cases did not happened during weekends or after holidays, but on Wednesday, Thursday and Friday. The authors justify this distribution with the increased mental and physical stress during the working days, which can increase sympathetic tonus, further enhancing the arrhythmogenic effect of alcohol. This study estimated that around 15-30% of idiopathic atrial fibrillation cases were related to alcohol abuse.\textsuperscript{15}
<table>
<thead>
<tr>
<th>Authors</th>
<th>Year of Publication</th>
<th>Design</th>
<th>Study sample</th>
<th>n</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ettinger et al.¹⁴</td>
<td>1978</td>
<td>Observational</td>
<td>Patients aged 25 to 62 years of both genders, admitted at Martland Hospital and Englewood Hospital between January 1972 and January 1976</td>
<td>32</td>
<td>Original description of HHS. Association between binge drinking and cardiac arrhythmias.</td>
</tr>
<tr>
<td>Engel et al.¹⁶</td>
<td>1983</td>
<td>Prospective observational</td>
<td>Men aged 43 to 75 years</td>
<td>14</td>
<td>Increased vulnerability to AF and atrial flutter after whisky ingestion.</td>
</tr>
<tr>
<td>Thornton</td>
<td>1984</td>
<td>Case series</td>
<td>Hospital-based, both genders, aged 34 to 47 years</td>
<td>4</td>
<td>AF induced by binge drinking in non-alcoholic people.</td>
</tr>
<tr>
<td>Koskinen et al.¹⁵</td>
<td>1987</td>
<td>Case-control</td>
<td>Consecutive patients aged 21 to 64 years, of both genders, admitted at Helsinki University Central Hospital between January 1 and 20 September 1985</td>
<td>100</td>
<td>A link between recent alcohol intake (previous 2 days) and atrial fibrillation was described. Weekend and Holidays prevalence of AF onset weren’t observed.</td>
</tr>
<tr>
<td>Wannamethee and Shaper²</td>
<td>1992</td>
<td>Cohort Prospective</td>
<td>Men aged 40 to 59 years selected at random from one general practice in each of 24 towns in England, Wales and Scotland</td>
<td>7735</td>
<td>Similar incidence of sudden death between occasional drinkers and heavy drinkers. Possible association between occasional binge drinking and sudden death.</td>
</tr>
<tr>
<td>Krishnamoorthy et al.¹⁷</td>
<td>2009</td>
<td>Case series</td>
<td>Patients aged ≤ 45 of both sexes, admitted at City Hospital, Birmingham between June 2000 and June 2006</td>
<td>88</td>
<td>20 patients reported alcohol consumption before onset of symptoms. Recurrences where observed in all patients who continued with ethanol abuse.</td>
</tr>
<tr>
<td>Mandyam et al.²⁹</td>
<td>2012</td>
<td>Case-control</td>
<td>Consecutive patients of both sexes presenting at electrophysiology laboratory at the University of California, San Francisco, Between September 2004 and March 2011</td>
<td>223</td>
<td>Patients with PAF had 4.42 bigger odds of reporting alcohol consumption before the PAF episode when compared to SVT group.</td>
</tr>
</tbody>
</table>
Although only indirectly related to HHS, Wannamethee and Shaper, in their prospective study about alcohol and sudden death, noticed that in patients aged between 40 and 49 without ischemic heart disease and with occasional drinking habits had a similar incidence of sudden death as heavy drinkers, suggesting that some of these occasional drinkers might have undergone binge drinking, which is associated with HHS, leading to cardiac arrhythmias that could result in sudden death.\(^5\)

Another retrospective study with young adults, by Krishnamoorthy et al, focusing not only on alcohol but also on illicit drugs, confirmed alcohol as a major trigger for atrial fibrillation. Out of 88 patients admitted with atrial fibrillation, 20 of them consumed alcohol before the onset of symptoms, although 1 of them also abused from cocaine. The same study followed-up some of the patients, verifying relapses in all those who carried on with alcohol abuse, which strengthens the abstinence as a prophylactic measure.\(^17\)

Mandyam and co-workers also observed an association between alcohol and PAF. This study had the particularity of comparing the PAF patients against patients with supraventricular tachycardias (SVT) in order to assess if alcohol intake precipitates PAF more frequently than would be expected by mere chance, because alcohol consumption is common and PAF is also quite frequent, so ethanol could appear to trigger PAF when the casual association is absent. Patients with PAF had a 4.42 higher odd of reporting alcohol ingestion before the PAF episode when compared to the SVT group.\(^29\)

**IV- Unsolved questions**

Although there were considerable developments about HHS, there are still some important questions requiring further research (Table 3):
IV.I- Long-term vs non-drinkers: do chronic drinkers have increased risk of HHS?

Although it is known that there is a link between chronic alcohol abuse and alcoholic cardiomyopathy, which is known to lead to cardiac arrhythmias, there has been considerable research, including several epidemiological studies showing an association between chronic alcohol consumption and increased risk of atrial fibrillation in apparently healthy individuals without evident heart disease, namely alcoholic cardiomyopathy. This link appears to be stronger for heavy abuse, but it is less clear for moderate and light ingestion.

Djoussé et al, using data from the Framingham study, have found a significant increase of AF risk (1.36, p=0.006) for chronic ethanol intakes >36g/day (around 3 drinks/day), however the increased risk was non-significant for amounts below that level.4 In a review paper about dietary factors including alcohol, by Gronroos and colleagues, a similar conclusion was drawn, with consistently significant increase of AF risk observed for heavy drinkers, but no increase with moderate alcohol consumption.10 An analysis of PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) study by Macfarlane et al, despite the sample being based on elder people, also found the alcohol intake was significantly higher in patients with AF than in those who did not develop AF.22

In a recent meta-analysis, Samokhvalov and co-workers, verified a dose-response relationship between the amount of alcohol drank daily and AF risk, with a relative risk of 1.08 per drink. However the risk of AF was only significant for intakes >3 drinks/day (36g/day) for men and >2 drinks/day (24g/day) for women, implying a possible threshold, above which there is a significantly increased risk of AF. Ingestions below those levels had the same risk as non-drinkers.11

One theory that can explain the lack of association of AF with moderate ingestion is that this kind of alcohol consumption may be protective against AF due to its anti-ischemic effects, protecting from possible cardiac events that can result in structural damage and lead to
Table 3 – Unsolved questions

- Long-term vs non-drinkers: do chronic drinkers have increased risk of HHS?
- Does the presence of cardiac comorbidities increase HHS risk?
- Is the incidence of HHS underestimated?
- Is there a genetic background associated with a higher susceptibility to alcohol arrhythmogenic effects?
- Does the type of drink affect the risk?
- Is there a threshold for acute alcohol intake above which the risk of HHS increases significantly?
- Do patients with HHS have a higher risk of thromboembolic events when compared to those with PAF independently from alcohol ingestion?
- Is the risk of HHS higher than the benefits of moderated intake?
- Does the speed of intake affect the risk of HHS? Does a faster intake increase the risk?
- Is the risk different if the binge drinking takes place during fasting or after a meal?

AF. However, in another recent meta-analysis, by Kodama and colleagues, apart from observing a dose-response relationship similar to the previously cited meta-analysis, their data also suggested that moderate intakes could have higher risk of AF compared to not drinking at all. More studies with bigger samples and follow-up are needed to clarify this matter.

Contrary to previous studies, a recent analysis from the Framingham study done by Shen et al did not observe a link between long-term alcohol consumption and AF. There was an increased risk for ethanol consumptions above 35g/day and 25g/day, for men and women respectively, but did not reach statistical significance. However, heavy drinkers were under-
represented which may have rendered this study underpowered for that purpose. A bigger sample and longer follow-up may be needed.\textsuperscript{30}

Overall the risk appears to be consistently increased for heavy chronic drinking, so one can wonder if this behavior increases the risk of HHS by superimposing binge drinking episodes in this already increased AF risk due to the chronic background.

Also, experimental studies with dogs have shown long-term alcohol abuse can lead to microscopic structural changes and cardiac conduction interferences before any clinical evidence of macroscopic structural heart changes\textsuperscript{21,31} These micro-structural and cardiac conduction changes might facilitate the occurrence of HHS after a binge drinking episode.

Another point is that chronic drinkers may be more prone to binge drinking, namely during holidays, weekends or other special occasions.

\textbf{IV.II- Does the presence of cardiac comorbidities increase HHS risk?} Previous studies suggest that in patients with cardiac disease that increases the chance of cardiac arrhythmias, namely atrial fibrillation, alcohol be a trigger of arrhythmia episodes.\textsuperscript{15,17} However further studies are needed to quantify this risk.

\textbf{IV.III- Other questions:}

-Is the incidence of HHS underestimated? HHS is most probably under-diagnosed since some of the cardiac arrhythmias, namely AF, can occur without symptoms.

-Is there a genetic background associated with a higher susceptibility to alcohol arrhythmogenic effects? For example Ettinger and colleagues related a case where the patient only had taken one drink before the onset of symptoms.\textsuperscript{14} These reports are also common on our daily practice.
-Does the type of drink affect the risk? There are many types of beverage: beer, shots, distilled drinks like vodka, whisky and others. So it’s important to know if some of these types of drink confer increased risk of HHS. For example beer was more frequently associated to alcohol as trigger of PAF than wine or spirit drinks in the study by Mandayam et al.29

-Is there a threshold for acute alcohol intake above which the risk of HHS increases significantly?

-Do patients with HHS have a higher risk of thromboembolic events when compared to those with PAF independently from alcohol ingestion?

-Is the risk of HHS higher than the benefits of moderate intake?

-Does the speed of intake affect the risk of HHS? Does a faster intake increase the risk?

-Is the risk different if the binge drinking takes place during fasting or after a meal?

**Conclusion**

Alcohol has a definite role in cardiac arrhythmias, either by chronic abuse or by binge drinking. It is important for physicians to recognize HHS and be aware of the role of alcohol in its genesis, sparing patients from complex investigations when there is no clinical evidence of cardiac pathologies.

During an admission of a patient with palpitations or other symptoms associated with cardiac arrhythmias, an highly suspicion of being HHS should occur if the patient exhibits signs of alcoholic intoxication or had a recent episode of binge drinking. After confirming the cardiac arrhythmia and excluding evident heart diseases, the physician should explain the syndrome to patient and recommend alcohol abstinence in order to prevent new episodes of HHS.
References:


Anexo I – Normas editoriais/orientações para autores do American Journal of Cardiology

MANUSCRIPTS are received with the understanding that they are submitted solely to THE AMERICAN JOURNAL OF CARDIOLOGY®, that upon submission, they become the property of the Publisher, that the work has not been previously published, and that the data in the manuscripts have been reviewed by all authors, who agree with the analyses of the data and the conclusions reached in the manuscript. The publisher reserves copyright and renewal on all published material, and such material may not be reproduced without the written permission of the Publisher. Statements in articles are the responsibility of the authors. The Journal does not accept original articles involving animal research.

As of May 1, 2005, all new manuscripts, including Readers' Comments and Errata, must be submitted through The American Journal of Cardiology online and review Web site (http://ees.elsevier.com/ajc). Authors are requested to submit the text, tables, and figures in electronic form to this address. The Publisher and Editors regret that they are not able to consider submissions that do not follow these procedures. Please include the corresponding author's phone and fax number. The cover letter should state precisely and concisely the significance and uniqueness of the work in the authors' view. The authors may state the extent of any concessions they are readily prepared to make (for example, the elimination of 1 or more figures or tables or a portion of the text) to increase the likelihood of publication of their work in the Journal. Several names and addresses should be provided of non-local experts who, in the authors' view, could provide objective and informed reviews of their work. The names of investigators considered unlikely by the authors to give nonbiased reviews of their work also may be submitted. This request is honored.

Please note that an editable file is needed for production purposes after acceptance, and we
ask that you submit source files in the case your manuscript is accepted.

Study recent past issues of the Journal for format. Arrange the paper as follows: (1) title page, which should include the title, the full names and academic degrees of the authors, and current affiliations of all authors; (2) abstract; (3) text; (4) acknowledgement; (5) references; (6) figure legends; ; (7) tables; and (8) figures. Number the title page as 1, abstract page as 2 and so forth. Type double-spaced (including references) with at least 25-mm (1-inch) margins, sized for 8.5 x 11 inch paper. Place 2 returns after every element, such as title, headings, paragraphs, figure captions, etc. Files should be labeled with appropriate and descriptive file names. Upload text, tables and graphics as separate files. Do not import figures or tables into the text document. Complete instructions for electronic artwork submission can be found on the Author Gateway, accessible through the journal home page.

**TITLE PAGE AND ABSTRACT:** For the complete title page, include the full first or middle and last names of all authors. List the current affiliations of all authors and link author names and affiliations by "a," "b," "c," etc., after the author names and before the affiliation. Provide information about grant support if necessary, including the location (city/state/country). If work described is supported by a grant from a pharmaceutical company, that fact should be stated on the title page. Add at the bottom the phrase "Corresponding author:" telephone number, fax number, email address, and mailing address. Add a **2-to 6-word** running head. Limit the abstract to 250 words. List **2 to 4 key words** for subject indexing at the end of the abstract.

**STYLE:** Use appropriate major **subheadings** throughout the body of the text, such as
Methods, Results, and Discussion. **Tables, figures, and references must be cited in numerical order throughout the manuscript.** Abbreviations are permitted, but usually no more than 5 per manuscript (at the Editor's discretion), and then they must be used on every page of the manuscript after they are initially spelled out (followed by the abbreviation) in both abstract and introduction. Abbreviations are usually limited to terms in the manuscript's title. Use generic names of drugs. Do not spell out any number, including those less than 10, except when used for opening a sentence, but try not to begin sentences with a number. Use symbols for less than (<), greater than (>) and percent (%). **Indent** paragraphs except for the first one in both abstract and introduction. Consult the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, published in The *Annals of Internal Medicine* June 1982;96:766-771, and also the *Stylebook/Editorial Manual of the AMA*.

**References:** List all authors, year, volume, and inclusive pages for all journal references, and specific page numbers for all book references as shown below. Do not use periods after authors' initials or after abbreviations for titles of journals. Check *Index Medicus* or *Annals of Internal Medicine* (June 1982) as cited above for journal titles and abbreviations. Personal communications and unpublished observations do not constitute references, but may be mentioned within the text. Articles with incorrect reference formats will not be processed. Do not use "et al" - names of all authors must be included. All references **must be typed out at the end of the article on a new page. Please do not use the footnote or endnote functions in your word processing program.**


**FIGURES:** Number figures in order in which they are mentioned in the text. Type figure legends on a separate page, double paced after the references. Clearly mark figures with a, b, c, top, bottom, right and left. Download each figure as a separate file (.tif or .eps formats are preferred, although .ppt, .xls, .pdf, and .doc files are accepted. jpeg files are acceptable for the review process only. They are not acceptable for publication. Do not import figures into the text document. Complete instructions for electronic artwork submission can be found on the Author Gateway, accessible through the journal home page. Submit written permission from the publisher and author to reproduce any previously published figures. Limit figures to the number necessary to present the message clearly. **Figure resolution must be a minimum of 300 dpi.** Type figure legends on a separate page, double spaced after the references. Identify at the end of each legend and in alphabetical order all abbreviations in the figure. The cost of color reproduction must be paid by the author.

**TABLES:** Number each table in Arabic numerals (Table 1, 2, etc.) and title each
table. **Download each table as a separate file.** Identify in alphabetical order at the bottom of the table all abbreviations used. When tabulating numbers of patients, use no more than 2 lines preferably only 1 line per patient. Use a plus sign (+) to indicate "positive" or "present" a zero (0) for "negative" or "absent" and a dash (-) for "no information available" or "not done." Do not use "yes", "no" or "none."

**READERS' COMMENTS:** The author who submits a "letter" should provide a cover letter to the Editor in Chief stating why the letter should be published. The letter (as well as references) should double-spaced, and limited, with few exceptions, to 2 pages. A title for the letter should be provided at the top of the page. At the end of the letter, the writer's full name and city and state (or country if outside the US) should be provided. The author's title and institution should not be included. A letter concerning a particular article in the *Journal* must be received (from authors within the US) within 2 months of the article's publication.

**REPRINTS:** Price schedules and order cards for reprints are mailed to the author upon publication of the article. Individual reprints must be obtained through the author.

**PERMISSIONS:** All inquiries regarding copyright material from this publication, other than reproduction through the Copyright Clearance Center, should be directed to Elsevier Ltd., P.O. Box, Oxford OX5 1DX, UK. Tel: (+44)1865 843830; Fax (+44)1865 853333; E-mail: permissions@elsevier.co.uk.