



# Atrial fibrillation in athletes: Implicit literature-based connections suggest that overtraining and subsequent inflammation may be a contributory mechanism

Don R. Swanson

*Division of the Humanities, The University of Chicago, Walker 003, 1115 E. 58th St., Chicago, IL 60637, United States*

Received 10 January 2006; accepted 10 January 2006

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**Summary** Research on atrial fibrillation (AF), a common heart arrhythmia in the elderly, over many decades has resulted in a literature of more than 16,000 articles indexed in Medline. An exploratory Medline search was conducted in which the subheadings for epidemiology and etiology of AF were combined to form a small subset of the initial records. Further computer-assisted selection led to a few articles that reported an unexpectedly high prevalence of AF in groups of otherwise healthy middle-aged endurance runners and other athletes. Why athletes should be unusually susceptible to AF is mysterious and puzzling.

Because relatively few articles are about both AF and endurance exercise, a computer was used first to create a list of important terms that these two separate literatures had in common. Several inflammation-related terms, including C-reactive protein (CRP) and interleukin-6, were on that list. Further searching and literature analysis revealed that excessive endurance exercise or overtraining can lead to chronic systemic inflammation and, separately, that there is a solid association between CRP and AF and that anti-inflammatory agents have been reported to lower CRP and ameliorate AF. No articles were found that brought together all three concepts – AF, inflammation, and exercise.

The following hypothesis is plausible, readily testable, and apparently novel: Older athletes diagnosed with AF but otherwise healthy who have engaged in rigorous aerobic endurance exercise for more than a decade will have CRP levels that are higher than those of a similar population of athletes without AF. Corroboration of this hypothesis would then justify a prospective clinical trial of anti-inflammation therapy. It is of particular interest to extend recent studies of inflammation in AF to athletes; athletic behavior that can induce inflammation may contribute to understanding the origins of AF.

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## Introduction

I describe here a (more or less) systematic literature-based approach to finding published medical

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*E-mail address:* [d-swanson@uchicago.edu](mailto:d-swanson@uchicago.edu).

hypotheses that seem both promising and neglected.

The medical problem chosen here as an example is atrial fibrillation (AF), a commonly diagnosed heart arrhythmia of mysterious origins that has been an object of study for over a century and has generated more than 16,000 articles indexed in Medline. AF is characterized by rapid chaotic electrical impulses of 300–600 per minute circulating within the atria and resulting in dysfunctional atrial activity and an irregular heart rate. Although many comorbidities and risk factors are known, as well as certain pathologies of the atria that predispose to AF, the ultimate underlying cause or causes are apparently unknown. AF is strongly age-related, with an incidence that doubles approximately every 10 years after age 50 [1]. Most patients are over 75, and it is this age group that has been the main target of clinical research.

The title of this paper notwithstanding, no assumption is made at the outset that athletes constitute a target population of interest. The target is to be discovered rather than assumed.

The method used is divided into two parts, with the following two goals: first, to find a plausible hypothesis that has not already been extensively researched, and, second, to discover new biological pathways or mechanisms relevant to the hypothesis.

## Method, Part I: A search for hypotheses

Part I is based on interactive search strategies for exploring the biomedical literature using Medline. The medical subject heading (MeSH) and subheading system constitutes the basis for indexing Medline records and for understanding the search process. There is an immense body of expert knowledge that has evolved over the past century and is embedded in the design of MeSH and its application to the indexing of Medline. To adequately exploit this built-in expertise requires a thoughtful and informed approach to the design of search statements and strategies [2]. MeSH and its subheadings provide tools and structure for exploratory searching. The following strategy is not intended as a formula or a method, but rather as one example of how subheadings can sometimes work together in pairs.

On the grounds that epidemiology might provide clues to the origin of a disease by identifying population groups at risk, AF was searched in Medline using the subheadings for epidemiology (ep) and etiology (et). The resulting co-occurrence yields only 243 records (as of 1 October 2005), a small subset of all records on AF.

Any hypothesis about AF must relate AF to something, and, here in Part I of the method, that “something” is treated as an unknown denoted by “X”, where X can be represented by one or more main subject headings, with appropriate subheadings. The strategy proposed here is to examine the values of X that result from different subheading specifications.

To pursue a single example, the subheading “physiology” (ph) is proposed and searched independently. Within any Medline record, the main heading to which ph is attached becomes a candidate for the unknown “X”. The 243 records from the ep-et Medline search above are next downloaded and become the input to a computer process that identifies and counts the co-occurring pairs (AF/et and X/ph, for all values of X), and selects those that occur only once for any specific X, thus indicating that the pair in question probably has not been extensively researched and reported. The hypothesis of interest here is that AF is connected with X, and so the (now very limited) output is visually screened to select only records with an interesting AF–X relationship.

The (unscreened) output for the present example consists of only 13 Medline records. The display is limited to the title preceded by the MeSH terms that carry the selected pair of subheadings, et and ph. Each record is identified by its PubMed ID number. The following three of the 13 records in the output are remarkable for identifying an unexpected population at risk for AF – namely, otherwise healthy endurance runners and others who had engaged in intensive long-term exercise:

- #1  
9624065 AtrialFibrillation/et Exercise/ph  
9624065 AtrialFibrillation/et Running/ph  
9624065 1998 Lone atrial fibrillation in vigorously exercising middle aged men: case-control study.
- #2  
11863350 AtrialFibrillation/et Sports/ph  
11863350 2002 Long-lasting sport practice and lone atrial fibrillation.
- #3  
12839069 AtrialFibrillation/et PhysicalConditioning, Animal/ph  
12839069 2003 Risk factors for atrial fibrillation during racing in slow-finishing horses.

It is now clear that at least one found “X” can be equated to the physiology of exercise, running, or sports – which now identifies the aforementioned target population, a key ingredient of an AF–X hypothesis.

In the earlier of the three papers above (#1) [3], a controlled study of top-ranked orienteers (runners – age 35–59) who had an average of 36 years of intense training was reported. Those who had ever been diagnosed with atrial fibrillation or atrial flutter had been identified by a questionnaire survey, and the diagnosis confirmed from their medical records. Defining “lone AF” as AF without structural heart disease or other known risk factors, lone AF had been diagnosed in 12 of 228 orienteers and in 2 of 212 controls ( $p = .012$ ), the relative risk being 5.5 in orienteers. The authors conclude that “vigorous long term exercise is associated with atrial fibrillation in healthy middle aged men despite protecting against coronary heart disease and premature death.” They speculate that “enhanced vagal tone, characteristic of endurance athletes, predisposes normal hearts to atrial fibrillation. Atrial enlargement and left ventricular hypertrophy, both features of the endurance athlete’s heart, may further increase the tendency to atrial fibrillation” [3, p. 1785].

The second study above (#2) [4], citing the Karjalainen work [3], developed supporting data showing that 32 men out of 51 (63%) with lone AF (average age 44) had been engaged in long term sport practice (av. 22 years) at least 3 h/week, mostly soccer, cycling, or swimming. The authors cite other data showing that, in the general population, only 15.4% of men between age 25 and 65 performed regular physical activity equivalent to 3 h of sports practice per week, significantly different ( $p < .01$ ) from the above 63% for the AF patients studied.

Other authors had earlier stated that AF incidence in competitive athletes is considerably higher than in the general population of the same age [5, p. 1384, 6, p. 203]. However, the same may not be true of younger athletes and it is reasonable to assume that age as well as number of years of intense exercise are important factors [7]. In any event, more systematic data are needed to establish whether the prevalence of AF in athletes who exercise at some specified level of frequency, duration, and intensity is significantly greater than that of the general non-exercising population of the same age and cardiac health status. At this point, the evidence is only suggestive, but enough so to stimulate further study of possible mechanisms and origins of AF in athletes.

## Two puzzling questions

Regular aerobic exercise leads so persuasively to cardiovascular health benefits that the appearance in runners and other athletes of atrial fibrillation

with even average, let alone excessive, prevalence, is mysterious and puzzling. Equally so is the question of whether we need a different explanation to account for AF in the typically much older non-exercising AF patient, or whether there are causal factors common to these two quite different populations.

## An unusual case report of a cure and a mechanism

A recent case report citing the Karjalainen paper [3] is worth noticing. Obel and Davidson describe a 53-year-old male endurance runner with symptomatic cardiac arrhythmias, including atrial ectopy and AF, but otherwise healthy. After 3 months of detraining and lighter exercise, the patient’s symptoms were ameliorated, atrial ectopy all but vanished, as did AF – these changes were sustained at a 6-month followup [8]. The authors state: “One mechanism by which long periods of intense physical activity can result in a propensity to atrial tachyarrhythmia is apparent from studies using prolonged rapid atrial pacing (PRAP) as a method of inducing sustained AF in animal models. Studies examining the effects of PRAP on the electroanatomic remodelling of the atria have shown that sympathetic hyperactivity occurs, which has a powerful influence on the maintenance of AF under such conditions” [8, p. 63].

A similar mechanism apparently can induce AF in humans; a study of 13 young olympic-class athletes with AF showed that AF could be triggered by transesophageal atrial pacing, and that it would disappear if the athletic activity is stopped for a long enough period of time (an average of 20 months in the group studied) [6,9]. Other studies in humans report that supraventricular tachycardia can lead to AF [10,11].

## Exercise-induced supraventricular tachycardia (SVT)

Yeh et al. showed that exercise provokes various types of SVT through several different mechanisms. Of particular interest, the authors conducted a study of 14 patients with reproducible exercise-provocation of SVT and observed that certain types of SVT were initiated when a “critical heart rate” is achieved during sinus rhythm, a rate that varied among patients from 80/min to 150/min. The same critical sinus rate was reached when SVT was provoked during isoproterenol infusion [12]. Exercise-induced SVT is strongly age-related [11,13].

Schoonderwoerd et al. compared atrioventricular pacing of goats for 4 weeks at a rapid atrial and ventricular rate (240 beats/min) with atrial pacing at the same high rate but with ventricular rate kept low and regular at 80 beats/min. They concluded that atrial structural remodeling, including atrial enlargement or stretch and other pathologies conducive to AF, was related primarily to the concomitant presence of a rapid ventricular rate rather than to atrial tachycardia alone [14]. Saffitz and Schuessler, in an editorial comment on this work, point out its implications for understanding the underlying substrates for AF and for defining potential new therapeutic targets [15]. Two reviews discuss various mechanisms of AF-mediated remodeling of atrial properties in a way that promotes AF maintenance and induction [16,17].

## Method, Part II: Finding new connections between AF and exercise

Earlier work on the analysis of complementary but disjoint literatures was based on searching for unnoticed indirect or implicit connections [18,19]. For the purpose of assisting such an analysis, a set of computer programs and processes called Arrowsmith was used [20,21]. Two somewhat different versions of Arrowsmith are publicly available for online use at: <http://kiwi.uchicago.edu> and <http://arrowsmith.psych.uic.edu>.

Arrowsmith is intended to enhance but not to replace human creativity in literature exploration, and its output depends critically on the quality of input in the form of Medline searches. In effect, Arrowsmith extends the power of a Medline search by processing its output in a way that helps the user identify potential biological pathways. The logic of that process is described briefly as follows.

The input to Arrowsmith consists of the downloaded results from two Medline searches (A,C); for example, A = the set of all records on athletic overtraining, and C = the set of all records on AF, with few or no articles common to the two sets. The main task of Arrowsmith then is to find all important terms, B (key words and phrases within the bibliographic records) common to the two separate sets of records (A,C), a task that cannot be performed using conventional database search techniques. Such bridging terms have the potential to become building blocks for biological pathways from A to C.

The main purpose of Arrowsmith is to find indirect or implicit connections between A and C that enhance the plausibility of an A–C relationship even in the absence of any appreciable number of

papers (in the intersection of sets A and C) that document direct connections. Enhancement of a proposed A–C relationship is the aim of the present paper.

The mechanisms or pathways by which A might influence C are called, collectively, B. Pathways A–B established within one set of articles and separate pathways B–C within a second, non-overlapping, set, suggest that bringing together these two fragments of pathway that share a B-term might reveal previously unnoticed implicit A–B–C pathways worth investigating. The Arrowsmith output normally reveals a large number of possible B-terms that might connect A with C. Arrowsmith provides a display of bridging terms and the titles they come from, putting AB and BC into a suggestive juxtaposition intended to stimulate the detection of plausible biological pathways from A to B to C. The idea of an implicit or hidden A–C connection was initially called “undiscovered public knowledge” [22,23], and later a “literature-based approach to scientific discovery” [24], or just “literature-based discovery” [25,26] – more generally it may be considered a branch of medical informatics.

In the present paper, attention is shifted to cases in which the A–C intersection is not a null set but contains instead just a few articles. Those few articles (such as #1 and #2 above) are likely to contain hypotheses that explicitly connect A with C, and may also report early tests of the hypotheses, irrespective of whether biological mechanisms or pathways have also been investigated or discovered. Published hypotheses about an A–C relationship, especially if there are only a few records common to A and C, can become the point of departure for an Arrowsmith-assisted search for plausible new pathways not previously documented.

Arrowsmith was used to find more connections between endurance exercise and AF, taking the previously listed #1 and #2 as “seed” articles for deriving new Medline search terms. The new search created input File A (2221 records) based on MeSH headings “running” or “exercise” with the sub-heading “physiology” (ph), and a number of title words related to endurance running. Input File C contains 1791 records with “atrial fibrillation” as both a title term and a MeSH term with the sub-heading “etiology” (et). The B-list (words and phrases that occurred in both the A-titles and the C-titles) consisted of 131 terms. Among them, four related terms are notable: C-reactive protein (CRP), inflammation, interleukin 6, and inflammatory, the first and third being well-known markers of inflammation. These four terms link endurance

exercise with inflammation and inflammation with AF. From their context in A-titles and C-titles (and subsequently from the articles themselves) the user can determine whether they enhance the plausibility of an AF-exercise connection. Evidence that the latter connection via inflammation has not before been noted in any other article covered by Medline is suggested by the fact that no single Medline record could be found that had all three index or search terms – atrial fibrillation, inflammation, and exercise – or their equivalents.

### Inflammation and normal intensive exercise

Many studies have demonstrated acute short-term increases in IL-6 and CRP released in brain, skeletal muscle, and/or connective tissue in response to intensive or prolonged exercise, particularly to long-distance running [27–30]. Increases in IL-1 receptor antagonist and in some anti-inflammatory cytokines were also detected [31,32].

Long-term systematic controlled training exercise in general results in a decline of inflammatory markers, putting aside questions of running injuries and overtraining. A 9-month study of 14 runners in training for a marathon showed a distinct downward trend in their baseline C-reactive protein (CRP) during the training period [33]. Two major reviews support the distinction between acute pro-inflammatory and long-term anti-inflammatory response in the case of normal intensive exercise [34,35].

### Inflammation and excessive intense long term exercise

Excessive training that results in deterioration of performance is called “overtraining”; similar to “burnout”. Lucille Smith in an extended analysis has hypothesized that systemic inflammation “is the central underpinning of the overtraining syndrome” [36, p. 320]. She argues that musculoskeletal trauma results in local inflammatory reactions; with continued and excessive high intensity training, local inflammation becomes chronic and systemic [36]. That overtraining entails immunological dysfunction has also been extensively argued [37,38]. Angeli et al. state “The most attractive hypothesis that accounts for the observed neuro-endocrine-immune dysregulation is Smith’s cytokine hypothesis of the overtraining syndrome” [38, p. 603] It should be stressed that, according to Smith’s cytokine hypothesis, one should expect increasing systemic inflammation only with overtraining, but not necessarily with a well-designed systematic exercise program.

More data are needed, however, on the systemic effects of long-term repeated overtraining in order to directly test Smith’s hypothesis.

For purposes of the present article, the idea of overtraining is extended to include the muscle and tendon overuse syndrome and the cycle of injury/reinjury, all of which can lead to chronic systemic inflammation. Perry has analyzed chronic inflammation from athletic injury and overtraining either in elite athletes or in unfit individuals exercising regularly, and points out the value of an active approach to rehabilitation that entails moderate levels of exercise [39]. A similar conclusion has been reached via immunological analysis. “A tentative trend may be discerned whereby light to moderate exercise may increase immune responsiveness but high-level competition sport, especially if it involves extensive endurance training, may lead to a degree of immunosuppression” [37, p. 518].

### Inflammation and AF

Engelmann and Svendsen at the University Hospital of Copenhagen have provided a substantial review of the English-language literature on inflammation, anti-inflammatory therapies, and AF, covering the period from 1990 to April 2005 [40]. Their conclusions are: [p. 2089].

1. Histological studies have demonstrated inflammatory infiltrates in [the atria of] AF patients and in animal models of AF.
2. Epidemiological studies have shown a solid association between C-reactive protein and both the presence of AF and the risk of developing future AF.
3. In case-control studies C-reactive protein is significantly elevated in AF patients and [negatively] associated with successful cardioversion. Moreover, C-reactive protein elevation is more pronounced in patients with persistent AF than in those with paroxysmal AF.
4. Treatment with glucocorticoids, statins, ACE-I, and ARBs seems to reduce recurrence of AF. Part of this anti-arrhythmic effect may be through anti-inflammatory activity.

Note: Bracketed phrase in “1” is inserted for clarification; bracketed word in “3” corrects an error.

The authors note several issues that require further investigation, including inflammatory parameters in patients before the onset of AF, and whether inflammation is an epiphenomenon of AF or a causal pathway [40,41].

More recent articles provide additional supportive data.

Dernellis and Panaretou conducted a randomized placebo-controlled prospective clinical trial of atorvastatin in a population of 80 patients with asymptomatic paroxysmal AF. After 4–6 months, the treatment group had lower CRP levels and a significant reduction in the number of episodes of PAF compared to the placebo group [42]. These same authors had earlier reported a similar trial using methylprednisolone to treat patients with persistent AF [40].

Psychari et al. found CRP to be an independent predictor of AF, and both CRP and IL-6 to be positively related to left atrial diameter and negatively related to left ventricular function. IL-6 was positively related to AF duration. The authors suggest that inflammation participates in the evolution of AF, and could have a role in atrial structural changes [43].

Malouf et al., at the Mayo Clinic, in a prospective study of 67 patients with AF or atrial flutter reported that high levels of CRP were predictive of an increased risk of recurrence of arrhythmia within one month after successful electrical cardioversion [44].

### **Inflammation as an implicit indirect literature connection**

It has been argued in the preceding two sections that long-term endurance exercise, if excessive, can induce systemic inflammation [36–39], and that, in a separate literature, inflammation has been associated with an increased risk of AF, or of changing atrial structure in a such a way that AF can be initiated, supported, and/or maintained. Moreover it has been reported that anti-inflammatory agents can reduce CRP and ameliorate AF [40–44].

However the search for any one article that presents both premises of the syllogism (exercise can lead to inflammation, and inflammation may lead to AF) turned up nothing, as indicated earlier, in that no single article could be found (in Medline) with all three terms.

### **Concluding hypothesis on AF in dedicated athletes**

Older endurance runners and other athletes who overtrain, resume training too soon after injuries (the “reinjury cycle”), or push their physiological limits, including heart rate, too far and too often, eventually can induce chronic systemic inflammation that may lead to atrial changes conducive to

AF. The new connection of inflammation suggests the following readily testable hypothesis:

Older athletes diagnosed with AF but otherwise healthy, who have been engaged in rigorous aerobic endurance exercise for more than a decade, will have CRP levels that are higher than those of a comparable group of athletes without AF.

### **Discussion of the hypothesis**

So far as can be determined, the foregoing hypothesis has not previously been proposed or tested.

A positive outcome would support inflammation as a possible contributory mechanism of AF in athletes, and so would justify and encourage a prospective clinical trial of anti-inflammation therapy in athletes with AF, perhaps similar to that of Dernellis and Panaretou in 2005 [42]. However, the possibility that continued excessive exercise behavior might then defeat the therapeutic aims of anti-inflammatory treatment makes it imperative to design the trial in a way that limits intensity, duration, and frequency of exercise in both the treatment and control groups.

A rationale for a well-controlled approach to graded exercise might be supplied by the “critical heart rate” that Yeh et al. [12] observed in some of their AF patients. If the existence of such a critical point can be further substantiated, it might then be used as a threshold marker for signalling prudent exercise limits.

Supporting evidence prior to conducting a long-term clinical trial might be obtained from tests using animal models of prolonged rapid atrial pacing to induce AF [8,14], comparing groups with and without treatment by anti-inflammatory agents.

Arguments have been given for two mechanisms that may lead to an influence of athletic overtraining on AF – a high ventricular rate, and the induction of chronic systemic inflammation. If indeed both mechanisms are present, it would be important to determine how and whether they are related. That intensive exercise may be a common origin of course should not go unnoticed. A few studies are suggestive of other possible connections [45–48].

### **Significance of this work: methodologic and medical**

This article has demonstrated, as did earlier published examples, the existence of complementary but disjoint literature pairs which, when brought

together, reveal unintended and possibly unnoticed connections of scientific interest. In a number of such examples, subsequent clinical and laboratory tests corroborated the literature-based connections we reported, as discussed elsewhere [21,49,50]. However the present article differs in method by focusing on the few articles that a not-quite-disjoint literature pair have in common, for these stand a good chance of containing relatively neglected hypotheses already recognized as plausible and that might benefit from new connections. In the context of literature-based discovery, the method here bypasses or finesses the difficult problem of open-ended discovery – in which only a single node (rather than the 2-node A–C) becomes the input to a discovery process. By assuming that there is an abundance of already published but more or less neglected hypotheses that can be brought to a more productive life by supplying new connections or pathways, the search problem becomes several orders of magnitude simpler than an open-ended search. The new process introduced might appropriately be called literature-based resurrection.

The medical significance of this paper derives from the outcome of the applied method, in which implicit literature-based connections have been found between excessive endurance exercise and AF. Corroboration of a pathogenetic chain of events that leads from exercise behavior to AF may contribute to a better understanding of the origins of AF.

## Acknowledgements

I thank Neil R. Smalheiser for many helpful suggestions and Vetle Torvik for his skilful enhancement of Arrowsmith techniques implemented at the University of Illinois – Chicago (UIC) website.

This work has been supported in part by a subgrant from the University of Illinois – Chicago (PI Neil R. Smalheiser, M.D., Ph.D.) R01 LM07292-05, Arrowsmith data mining techniques in neuro-informatics, co-sponsored by NLM and NIMH, 15/6/01–31/5/06.

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