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Running, esophageal acid reflux, and atrial fibrillation: a chain of events linked by evidence from separate medical literatures

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Abstract

Using a previously described approach to generating novel medical hypotheses, this paper shows how two separate medical literatures taken together can suggest new information not apparent in either literature alone.

Many studies have demonstrated that aerobic exercise in healthy people can induce esophageal acidic reflux that increases with the duration and intensity of exercise. Separately, independently of exercise, it has been shown that, in patients with gastroesophageal reflux, esophageal acid exposure can lead to atrial fibrillation (AF) and to other heart dysrhythmias. The two arguments together suggest that a regimen of excessive exercise may be conducive to AF mediated by acid reflux, an implicit, but unpublished, hypothesis.

Proton pump inhibitors are widely used to treat gastroesophageal reflux. Remarkably, several small clinical trials of these drugs have been shown also to reduce symptoms and frequency of AF episodes in patients with comorbid acid reflux. Plausible mechanisms have been suggested. These small scale tests in a highly restricted population may be of particular interest in the light of a possible exercise-reflux-AF causal chain of events in a broader population of athletes. Because the minimum degree of esophageal acidity exposure required to induce AF is unknown, further tests of proton pump inhibitors for that purpose are therefore merited without regard to any known prior reflux in a population of runners with lone AF.

The prospect of reducing AF burden with a relatively benign agent is attractive in view of the limited options for effective treatment otherwise available. The study of arrhythmia and esophageal reflux in athletes may offer insights on the origin and natural history of lone atrial fibrillation.

Keywords

atrial fibrillation; gastroesophageal reflux; proton pump (antagonists & inhibitors); Medline; inflammation; autonomic nervous system; running; exercise; Arrowsmith; hypothesis generation; complementary literatures

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INTRODUCTION

An earlier analysis of atrial fibrillation (AF) in athletes combined arguments from separate medical literatures, one literature providing evidence that athletic overtraining can induce chronic systemic inflammation, and the other showing that inflammation may be important in the pathogenesis of AF (1). The two arguments together suggest that inflammation as a mechanism might explain an unexpected susceptibility of athletes to AF, unexpected because the typical AF patient is much older (median age 75) and sicker, with other heart diseases.

The present paper is based on the same approach to identifying implicit connections between separate literatures, an approach that is designed to stimulate new hypotheses of scientific interest. Many authors have provided evidence that vigorous aerobic exercise can induce gastroesophageal reflux (GER). Separate evidence not based on exercise shows that acidic GER may lead to AF and to other heart dysrhythmias, and that proton pump inhibitors may ameliorate both acid reflux and AF. The mutually isolated literatures that support these two arguments will be further explored and their arguments combined to show why athletes and others who engage frequently in vigorous exercise may be susceptible to AF even if otherwise they are in excellent cardiovascular health.

METHOD

Finding novel connections between complementary literatures

The approach described here is based on the idea that two scientific articles, or two non-overlapping sets of articles, can be complementary, in that, taken together, they suggest new information not apparent in either set alone. To find such pairs of complementary literatures depends in general on finding pairs of statements from different articles that are linked by key words or phrases that they have in common. Sets of articles are identified by exploratory searching of Medline, and key words and phrases shared by the separate sets are identified by a computer-assisted process called Arrowsmith.

The input to Arrowsmith, for the present study, consists of the downloaded results of two Medline searches, one a set of 2818 records on the physiology of vigorous exercise and the other a set of 2194 records on the etiology of AF (called Files A and C, resp.). The two Medline searches, conducted in Feb 2008, were updated versions of the same searches reported previously (1), defined by the following search strategy:

Database: Ovid MEDLINE(R) [1950 to Feb week 1 2008]

1. exp atrial fibrillation/et (3413)
2. atrial.ti. (38106)
3. 1 and 2 (2194)
4. (runn\$ or endurance or overtraining or vigorous or cycling or soccer or basketball or orienteer\$).ti. (16372)
5. (distance or marathon\$ or ultramarathon\$).ti. (8812)
6. exp exercise/ph or exp running/ph (22632)
7. 6 and (4 or 5) (2818)
8. 3 and 7 (0)

(et, ph are subheadings for etiology and physiology, resp.; ti=title; exp (“explode”) means: include all terms subordinate to the main heading addressed; subheadings retained unaltered.)

Sets 7 and 3 correspond to Files A and C, respectively.

The null set 8 shows that Files A and C have no records in common.

The above search is limited to titles and is restricted by set 6, so is not designed to be comprehensive. The goal is to find something rather than everything.

Arrowsmith was then used to find “B-terms” -- that is, key title words and phrases, and author names, that A and C have in common, producing as output in this case a ranked B-list of 186 terms. Each B-term is displayed together with the A- and C-titles in which it occurs. Whether the B-term link is biologically meaningful must be judged by the user from the contexts in which it appears. Juxtaposed A and C titles that have B-terms in common are intended to stimulate the user to see potential implicit complementary relationships (A–B vs. B–C) that may merit further exploration. The B-list is ranked by an algorithm that depends on the number of medical subject headings that the corresponding A and C records have in common, the higher weight indicating that the A and C records are more similarly indexed (and so in general more closely related in biological meaning). B-terms might also stimulate new Medline searches. Here, the top-ranked 7 terms on the B-list are:

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No. titles in A = 2818; No. titles in C = 2194
col 1=weight for each B=(100*#MHB common to A,C)/sqrt(nA*nC).
Weight  nA  nC  B-title-terms (words or phrases).
  300    1   1  endotoxemia inflammation
  200    1   1  doppler transmitral
  200    1   1  endothelial dysfunction
  200    1   1  adriaenssens_b
  200    1   1  proton pump
  200    1   1  sarcoplasmic reticulum ca2
  150    2   2  pulmonary venous
(nA=no. records in A; nC=# recs in C; #MHB=# MeSH terms in common;
Each B-term is a link to the corresponding title display).
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Further information about Arrowsmith is provided elsewhere (1 p.1088-92, 2).

RESULTS

Results of Arrowsmith search

Among the top 7 B-terms, “proton pump” is immediately of interest because of its possible clinical relevance. It is linked to an output display of the following two titles, each containing the phrase “proton pump inhibit--”.

A-title: Proton pump inhibition prevents gastrointestinal bleeding in ultramarathon runners: a randomized, double blinded, placebo controlled study. (3)

C-title: Case of paroxysmal atrial fibrillation improved after the administration of proton pump inhibitor for associated reflux esophagitis. (4)

The reported effect of PPIs on AF is surprising enough to stimulate a further search of Medline for other similar reports. A Medline subject-heading search for records with AF AND proton pump/ai (antagonists & inhibitors) then led to three articles (4, 5, 6). The first record (4) is the C-title above that triggered the search; the two new titles that emerged are:

“Reflux esophagitis in the pathogenesis of paroxysmal atrial fibrillation: results of a pilot study” (5).

“Treatment of esophagitis/vagitis-induced paroxysmal atrial fibrillation by proton-pump inhibitors” (6).

The Arrowsmith B-list output display also includes a link to the abstracts, from which it is clear that these two articles, as well as the Nakamura article (4) cited, all involve using PPIs to treat gastroesophageal reflux (GER) (a standard form of therapy for GER). From this result, GER can be seen as a plausible B-term, and indeed “reflux” is on the B-list, although at #93 was too far down the list to have attracted attention initially -- the ranking system being only approximate. The output titles to which it is linked are:

A-title: Esophageal reflux in conditioned runners, cyclists, and weightlifters (7).

C-title 1: Gastroesophageal acid reflux as a causative factor of paroxysmal atrial fibrillation (8).

C-title 2: Reflux esophagitis in the pathogenesis of paroxysmal atrial fibrillation: results of a pilot study (5).

The A-title associates running with esophageal reflux and there are now four C-titles above that associate esophageal reflux with paroxysmal AF, thus suggesting a potential complementary relationship, A–B and B–C implying A–C. This title-based implicit connection between running and AF (via GER) is at least suggestive enough to warrant further investigation.

Moreover, the implication appears to be novel. Even a broad Medline search (with the goal of finding everything rather than just something) turned up no articles that had all three concepts of interest: exercise, GER, and AF (i.e. A,B,C), thus showing that, in all likelihood, no explicit relationship between A and C via B has previously been documented.

Arrowsmith as a guide to further Medline searching

Arrowsmith is not, nor is it intended as, a method of automatic discovery, but rather as an aid to exploratory Medline searching, where the goal is to find complementary literatures, beginning with a well-formed problem such as finding a previously unknown cure or cause of a specified disorder. The B-list and associated title display is a point of departure for further searching of Medline. Once plausible complementary literatures are initially postulated from pairs of titles, it is usually necessary then to extend the original Medline search to a broader base in order to develop more fully the connection of A with B (here, exercise with GER) and the connection of B with C (i.e. GER with AF); results shown in the next two sections.

Elaborating the exercise-reflux connection (A–B)

Collings et al reported a study of 30 conditioned athletes showing that strenuous exercise induces significant reflux and related symptoms, and that reflux worsens after eating even a light meal (7). In that study, esophageal acidity was investigated in 10 healthy fit runners (7 were asymptomatic) following 80 minutes of moderate to hard running, during which they developed mild GER symptoms. Percentage of time with intraesophageal pH<4.0 was 4.9% for fasted runners and 17.2% for runners fed a light breakfast 1h before the run (7). An earlier study had also compared esophageal acidity in fed and fasted runners using a 24h ambulatory monitor and percent of time pH<4.0 as a defining criterion for acid reflux. GER occurred in 5 of the 11 fasted runners and 8 of the 9 fed runners during or just after exercise (9).

Soffer et al in two separate papers compared response to exercise in 8 trained cyclists with the response in 9 untrained subjects. Each time that pH dropped below 4.0 was counted as a reflux episode. Exercise was in a fasted state. The contrast between trained and untrained athletes is striking. The mean number of episodes per hour at VO₂max of 75% and 90%, resp., = 1.2, 3.7 episodes/hr for trained cyclists, but nearly 4 or 5 times as many for

untrained athletes, at 4.5 and 17.5 episodes/hr, resp. None of the trained cyclists experienced symptoms (10, 11).

Kraus et al (12) reported that 9 of 14 subjects developed GER during 1h of running (1 also did so during a baseline measurement). The number of subjects without reflux dropped from 6 to 4 to 2 as the pH criterion for defining reflux was increased (i.e. acidity decreased) from 3 to 4 to 5. That a drop would occur is self evident, but apparently few data that quantify the dependence on the pH criterion have been published.

In another study, 6 of 16 runners developed esophagitis, as shown by endoscopy, following a 20K race (13). Separately, 30 minutes after a light meal, a 30min run at an intensity of 70% VO₂max led to 6 episodes of GER in 12 runners and none in controls (14).

The foregoing studies have involved relatively few subjects so cannot reliably be extrapolated to larger populations. Several reviewers have, however, cited surveys reporting that, in larger populations of endurance athletes (in one case, a survey of 606 well-trained sportsmen), on the order of 36% to 67% have complained of upper GI symptoms characteristic of GER (15, 16).

In sum, exercise can induce acid reflux, reflux increases with the intensity and duration of exercise, and is worse after meals or in a state of dehydration. In all studies cited above, acidity determined by intraesophageal pH monitoring is taken as a definition and measure of GER. In a number of studies, symptoms were not well correlated with acid exposure.

A variety of reflux mechanisms have been suggested or investigated, including reduced gastric motility and absorption, decreased esophageal acid clearance, reduced or disorganized peristaltic esophageal motility, lower-esophageal sphincter relaxation, and reduced GI blood flow (15). Susceptibility to exercise induced GER may depend strongly on the structural integrity of the esophogastric junction (particularly the flap valve) (17).

Proton pump inhibitors (PPIs) are widely reported as beneficial in the treatment of exercise-induced GER (15, 16, 18).

Elaborating the reflux-AF connection (B–C)

Weigl, Stollberger, et al (5, 6) reported a pilot study of 18 patients with lone vagal PAF and retrosternal and epigastric pain. Gastroscopic examination showed that 14 patients had esophagitis and the other 4 had Barrett esophagus. Following therapy with a PPI, not only the epigastric pain and inflammation subsided but, remarkably, also PAF-related symptoms in 14 of the 18 patients. A follow-up electrocardiogram showed sinus rhythm in all patients. Because of the decrease of PAF, beta blockers or propafenone were discontinued in 5 patients 4 to 32 weeks after discontinuation of PPI therapy (5,6).

These authors suggest that inflammation may play a central role in the pathomechanisms of PAF due to GER, and they propose five possible pathways, including the effect of a local inflammatory process on vagal nerves adjacent to the esophagus (5,6). If they are correct that inflammation plays a central role in the apparent relationship of GER to PAF, then in athletes a chain of events from excessive exercise to GER to inflammation to AF may be postulated (1).

Two single-case studies also have reported that treatment with a proton pump inhibitor (PPI) not only was beneficial in reducing acidic GER but in substantially reducing the frequency of AF episodes (4, 8).

The effects of acidic GER on heart arrhythmias were investigated by Cuomo et al. in 32 patients with GER symptoms and idiopathic supraventricular dysrhythmias (6 patients with paroxysmal AF) (19). Nine patients with GER only, served as controls. The aim of the study was to determine whether acid reflux alters neurocardiac function and whether acid suppression affects the dysrhythmias. All patients underwent simultaneous 24-hour measurements of esophageal acidity and ECG monitoring. The high and low frequency components of the heart rate variability power spectrum, and their ratio (LF/HF), were calculated for each person. In 18 of the 32 patients with dysrhythmia, but none with GER only, the esophageal pH and the LF/HF ratio were strongly and significantly correlated over a 24h time period. The correlation in each of 12 patients was positive, and negative in each of the remaining 6 patients, apparently supporting the often-suggested dichotomy of vagal vs sympathetic dominance in AF. Following a 3 month course of PPI therapy (esomeprazole 40mg/day), cardiac symptoms were reduced in the patients for whom pH and LF/HF were correlated (19).

The LF/HF ratio is a measure of sympatho(LF)/vagal(HF) balance; the apparent preponderance of vagally mediated AF in the above data is consistent with Coumel's observation some years earlier that vagal influences on AF are predominant in the absence of heart disease (20). (Cuomo et al had excluded patients with organic heart disease from the group they studied (19)). The Cuomo findings of vagal dominance are also consistent with the Weigl data on lone vagal PAF (5), with the Nakamura report (4), and with a report by Mont et al that athletes have a greater tendency to experience AF under vagal stimulation than do non-athletes (21). Coumel, in an editorial comment calls attention to this finding of Mont and to the "adrenergic paradox" it appears to entail (22).

In sum, Cuomo et al concluded that they had identified a subgroup of patients with idiopathic heart dysrhythmias in whom esophageal acid stimulus elicited cardiac autonomic reflexes. Acid suppression improved both GER and cardiac symptoms (19).

Another study of atrial arrhythmias co-occurring with esophageal acidity in 3 patients was also reported. A 24 hour Holter was used to monitor arrhythmias and, simultaneously, an esophageal probe was used to monitor acidity. Arrhythmias and pH were significantly correlated in each patient; both esophageal acid exposure and atrial dysrhythmias, and their symptoms, diminished with omeprazole therapy. The authors suggest that esophageal reflux may be a causal mechanism in stimulating atrial arrhythmias, and that neural mechanisms via the parasympathetic pathway are likely to play a key role (23). This suggestion is consistent with the findings noted above.

Autonomic regulation also has an important role in both the initiation and termination of paroxysmal AF (24). The mechanisms by which AF is induced, particularly as shown from animal experiments, are further discussed in a recent review of autonomic function in AF (25).

DISCUSSION

The purpose of this article is not only to call attention to a perhaps previously unnoticed connection between running and AF via GER, as a basis for stimulating a new medical hypothesis, but also to suggest an approach to testing the hypothesis, particularly with respect to a suitable population of subjects and a clinical endpoint.

Comments on AF burden as an endpoint in clinical trials

To an increasing extent the criterion of AF burden (defined as percentage of total time in AF) is used as a measure of treatment outcome, particularly in clinical trials of AF ablation

and pacemaker procedures. Numerous difficulties, including long followup periods, are associated with more conventional outcomes such as morbidity, mortality, stroke, cardiac events, or symptom monitoring (26). AF symptom monitoring is unsatisfactory because asymptomatic episodes may be far more frequent than symptomatic, even among patients who also have symptoms (27).

Because very low burden is likely to go undetected, especially if most AF episodes are asymptomatic, it is important to conduct tests of therapies in population-based cohorts. It is plausible to assume that AF burden will vary widely, and that very low rates will disproportionately escape detection. At the same time, it is likely also that very low AF-burden rates have escaped most clinical investigations of cardioembolic stroke, the most important risk of AF.

A recent review by Wyse has examined several points of controversy concerning anticoagulation, including the important question of whether paroxysmal AF entails the same risk of stroke or systemic embolus as does continuous AF (28). He cites work by Capucci et al as evidence that brief episodes of self-terminating AF have a lower risk of stroke than has long-lasting AF (29). Capucci et al studied predictors of embolic events in 725 AF patients with implanted antitachycardia pacemakers. Among 303 patients with AF occurrences longer than 1 day (device-detected during a median 22-month followup) 10 developed an arterial embolism. Among the other 422 patients only 4 developed an arterial embolism. (3.1 hazard ratio, 95% CI 1.1 to 10.5, $p=0.044$). (29, Table 3).

It is not yet possible to define well-supported anticoagulation strategies for runners with low AF burden (e.g. in a range of 1% to 20%), particularly taking into account the increased risk of running-induced hemorrhage (3). To determine the clinical implications of AF burden merits a high priority in research on episodic atrial fibrillation. At least one major study is already underway, the purpose of which is to assess the risk of stroke and systemic embolism in pacemaker patients without a previous history of AF but who have brief atrial high-rate episodes (30). Even in this study, the choice of pacemaker patients over age 65 suggests that the population studied is likely to have more serious heart pathologies (e.g. AV-node disease) than the typical runner with AF.

The low-AF-burden healthy runner presents new research challenges that may have a bearing on the origin of AF, for the ranges of both age and AF-burden offer an opportunity to observe AF *in statu nascendi* and its ensuing natural history.

New ECG technology for AF detection

Although measurement of AF burden in the past has depended largely on implanted devices, a recent innovation in ambulatory ECG monitors, Medicomp's CardioPAL SAVI with AF burden, as well as their recent release of Decipher Holter, may be of great interest -- particularly for screening population-based cohorts. A software algorithm that automatically captures a complete arrhythmia profile based on rate, rhythm morphology, and p-wave abnormalities, yields data for calculating AF burden over a multiple-week period, irrespective of symptoms (31, 32).

Concluding hypothesis and comments on runners as a test population

Within a population of long-distance runners with PAF, proton pump inhibitors will reduce the frequency and/or duration of atrial fibrillation episodes (i.e. reduce AF burden).

The hypothesis as stated merits a test independently of any attempt to measure esophageal acid exposure, by first screening all runners for AF, administering PPIs for a defined period, then measuring the change in AF burden. Because excessive levels of duration or intensity

of exercise are more likely to induce GER, and the question of what is excessive is relative to age and physical condition, a test of the above hypothesis may be more sensitive in populations of older runners. AF is well known to be strongly age-related and a progressive increase with age of severe erosive esophagitis has also been reported (33). Almost all long-distance road races, at least in the U.S., including marathons, report results by 5-yr age and gender groups, making it convenient to identify similar populations and to control important variables such as training and physical conditioning regimens.

Most AF detected in a population of long-distance runners is likely to be lone AF -- i.e. AF without other heart pathologies. Chambers has cited evidence that lone AF tends to occur largely in physically fit middle-aged males, many of whom are fervent in their pursuit of sports, and has postulated a division of AF into two distinct types -- lone AF and pathologic AF, the latter in an older age range. He further suggests, citing supporting data, that the two types of AF can be differentiated by certain anthropometric parameters, and are distinguished by various physiologic and pathologic markers (34). Choosing a population of long-distance runners from road-race participants screened for AF, as outlined above, would provide an opportunity to contribute data relevant to several of Chambers' interesting hypotheses.

Comment on esophageal acid exposure criteria

The degree of acid exposure is usually expressed as a continuous variable based on percent of time that intraesophageal pH is less than 4.0. Two important questions appear not to have been systematically addressed in the literature -- namely, what minimal level of esophageal acid exposure, in terms of both frequency and duration, is sufficient to induce AF, and why should pH=4.0 (rather than, say, 4.5 or 5.0) be taken as a criterion threshold? The hypothesis and test defined above offers an opportunity to answer both questions, while also limiting the number of patients to be tested with the invasive procedure required to monitor acidic GER. The latter population can be limited to those known to have AF and to have responded favorably to PPIs.

Methodologic and clinical significance of this paper

I have shown, as one of an ongoing series of examples, how a computer-assisted process, interwoven with exploratory searching of Medline, can stimulate the creation of novel hypotheses -- by assembling and displaying fragments of published information that fit together suggestively. In this case, information on exercise-induced acid reflux was brought together with, and displayed next to, information showing that acid reflux (independently of exercise) may cause or trigger AF, to suggest a possible mechanism for AF susceptibility in long-distance runners.

The prospect of being able to define criteria for a new mode of therapy -- proton pump inhibitors -- for people with atrial fibrillation who engage in vigorous physical exercise, such as distance running, is attractive in view of the limited options for effective treatment otherwise available. Moreover, to study atrial arrhythmias in relatively healthy runners may help throw light on the origin and early natural history of lone AF.

Caveat

Although generally considered safe, the proton pump inhibitors pantoprazole and esomeprazole were recently reported to reduce human heart contractility (both atrial and ventricular), in vitro. The authors speculate on the clinical relevance of this finding, suggest particular caution in the case of patients with heart failure or severe liver impairment, and state that they have initiated a clinical study (apparently the first of its kind) to investigate

cardiac side effects of pantoprazole in healthy volunteers (35). The possibility that PPIs may act directly on cardiac tissue is notable.

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Abbreviations

AF	atrial fibrillation
PAF	paroxysmal atrial fibrillation
GER	gastroesophageal reflux
GI	gastrointestinal
PPI	proton pump inhibitor

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