

THE AFIB REPORT

Your Premier Information Resource for Lone Atrial Fibrillation!

NUMBER 27

MARCH 2003

3rd YEAR



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Many afibbers, myself included, have noted that it feels like something is building up in the body that is eventually released by an episode. Some, again myself included, have also noticed an increase in PACs and/or PVCs in the days prior to an episode and a total lack of ectopic beats in the first few days following an episode. Yet others have noticed a distinct pattern to their episodes in that they occur more or less every week, every 12 days, every 16 days or whatever. Finally, many afibbers have noticed a distinct increase in urination frequency during the early stages of an episode.

All these observations point to a hormonal connection. Something builds up in the body to set the stage for an afib episode. The episode itself gets rid of this "something" and then the cycle begins again.

In this issue we will explore one possible hormonal connection, namely that between the renin-angiotensin-aldosterone system, and its counter hormones, the natriuretic peptides. Please bear in mind that a connection between LAF and these two opposing hormone systems has not been proven or even investigated in clinical trials, so it is pure speculation at this point. Nevertheless, even if this particular hormone connection turns out to be a dud I hope that "rattling the hormone cage" may bring forth other possible hormone connections and ultimately lead us closer to a solution to the LAF puzzle.

Just a reminder - if you haven't already done so, don't forget to get your copy of my recent book "Lone Atrial Fibrillation: Towards A Cure" at www.afibbers.org/lafbook.htm - it provides a wealth of information on dealing with LAF.

Enjoy!

*Wishing you lots of sinus rhythm,
Hans Larsen*

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Aldosterone: Villain of the Peace?

It is likely that LAF only develops when three conditions are met:

- 1) The autonomic nervous system is dysfunctional.

- 2) The heart tissue is abnormally sensitive and capable of being triggered into and sustaining an afib episode.
- 3) A trigger or precipitating cause capable of initiating an episode is present.

An abnormally sensitive heart tissue, if triggered, becomes a source of premature atrial complexes (PACs) or ectopic beats that, if frequent enough, may run together to create atrial fibrillation. German researchers have recently confirmed that the majority of afib episodes are preceded by a series of premature atrial beats. The origin of these beats is the left atrium in almost 80% of all cases[1].

Unfortunately, the fact that we know how afib episodes begin has not produced an effective non-surgical means of preventing an episode. Most LAF episodes are paroxysmal or intermittent in nature. In other words, they do eventually stop. Perhaps if we knew what made them stop we could gain further insight into their mechanism and thus eventually come up with an effective prevention strategy.

Many afibbers, myself included, have noted that it feels like something is building up in the body that is eventually released by an episode. Some, again myself included, have also noticed an increase in PACs and/or PVCs in the days prior to an episode and a total lack of ectopic beats in the first few days following an episode. Yet others have noticed a distinct pattern to their episodes in that they occur more or less every week, every 12 days, every 16 days or whatever. Finally, many afibbers have noticed a distinct increase in urination frequency during the early stages of an episode.

All these observations point to a hormonal connection. Something builds up in the body to set the stage for an afib episode. The episode itself gets rid of this "something" and then the cycle begins again. To explore what might be going on in the body, it is necessary to first gain a rudimentary understanding of hormones.

Hormones 101

The body communicates with its individual cells through the nervous system and the endocrine system. Among the most important functions of this communication is the regulation of metabolism and energy balance, regulation of the chemical composition and volume of the extracellular fluid (internal environment), maintenance of homeostasis, regulation of the heart beat and muscle contractions, activation of the immune system, and the control of the secretions of various glands.

The autonomic nervous system (ANS) transmits its messages through the release of norepinephrine (noradrenaline) and acetylcholine from sympathetic and parasympathetic nerve fibers respectively. The ANS can often take care of relatively minor perturbations in the system and does so almost immediately. However, if major adjustments are needed the endocrine system springs into action. The endocrine system uses hormones to transmit its messages to the organ where an adjustment is required. The hormones themselves are produced in the endocrine glands among which the adrenal glands, the thyroid gland, the pituitary gland, the hypothalamus, the pancreas, and the parathyroid glands are probably the most important. Important hormones are also produced in the testes, ovaries, stomach, small intestine, kidneys, and the thymus and pineal glands.

The path taken to produce a hormone is often quite tortuous. For example, the release of cortisol is initiated in the hypothalamus region of the brain. Corticotropin-releasing hormone (CRH) is produced in the hypothalamus in order to carry a message to the pituitary gland to produce and release adrenocorticotrophic hormone (ACTH) that, in turn, is carried in the blood stream to the outer parts of the adrenal glands. The outer part (cortex) of the adrenal glands initiates the manufacture of cortisol, which upon entering the blood stream proceeds to the liver and causes the release of glucose.

Hormones often work in pairs. Insulin, for example, arranges for glucose to be stored as glycogen while its counter hormone, glucagon, initiates the conversion of glycogen back to glucose. The hormone calcitonin decreases the level of calcium in the blood while parathyroid hormone increases it.

The endocrine glands release their hormones (chemical messengers) into the blood stream through which they reach every cell in the body. However, and this is a very important point, the hormones and neurotransmitters

(norepinephrine and acetylcholine) can only act on cells that are equipped with receptors to receive them. Some types of hormones bind to receptors on the surface of the cell while others must go through the cell membrane in order to act on its receptors, which can be located in the liquid phase of the cell (cytoplasm) or in the nucleus itself.

Most cells have receptors for several different hormones and may contain as many as a million copies of a certain type of receptor. The receptors are specific to a particular hormone, but may, in some cases, also accept hormones of a closely related molecular structure. Once the hormone has “docked” with its receptor it initiates a protein synthesis resulting in the desired effect (eg. glucose storage or release).

Hormone receptors are important targets of pharmaceutical (and other) drugs. Some drugs are designed to activate the receptors while others block them (beta-blockers, for example). Yet other drugs prevent the “spent” hormones from being returned to their source or from being broken down, thus maintaining an artificially high extracellular concentration of the hormone. The much used serotonin reuptake inhibitors (SSRIs) like Prozac and Paxil are examples of this type of drug.

Hormone production and release are also regulated through natural feedback loops. For example, once cortisol has done its job a message goes back to the pituitary gland to stop the production of ACTH, the hormone directing the adrenal cortex to produce cortisol.

It is clear that the endocrine system is extremely complex and very powerful and it would indeed be odd if it did not, in some way, enter into the equation governing afib episodes.

The Hormone Connection

Ever since man emerged from the primordial sea, the maintenance of a finely tuned saline environment inside our body has been of primary importance. The balance of sodium and water, and consequently the blood pressure, is controlled by the action of two opposing hormone systems, the natriuretic peptides and the renin-angiotensin-aldosterone system (RAAS). The natriuretic peptides cause excretion of salt (Na+) and water in the urine while the RAAS hoards salt and water through its action on the kidneys. Of particular interest is the fact that an overactive RAAS will lead to both potassium depletion (hypokalemia) and magnesium depletion (hypomagnesemia)[2]. Low potassium and magnesium levels are potent initiators of PACs and thus may precipitate LAF episodes.

Could it be that paroxysmal afib is the result of a tug-of-war between the natriuretic peptides and the RAAS with an overactive RAAS initiating an episode and the natriuretic peptides terminating it? Let us ponder the evidence.

Natriuretic Peptides

There are three natriuretic peptides - atrial natriuretic peptide formed during stretching of the walls of the atria, brain natriuretic peptide formed by stretching of the walls of the ventricles (it was first isolated in the brain of a pig, hence its name), and natriuretic peptide C caused by stretching of the arterial walls. The stretching normally comes about through pressure exerted by higher than normal fluid (blood) volume; however, in the case of LAF the peptides are released due to the violent “shaking” of the walls of the atria and ventricles during an afib episode rather than due to increased fluid volume (hypertension).

The release of atrial natriuretic peptide (ANP) usually results in increased urination during the early part of an LAF episode. The link between ANP and LAF has been thoroughly studied and several important findings have emerged:

- ANP levels are lower in people with LAF than in “normal” people;[3]
- ANP levels decline with age and increased duration (years) of afib. This is probably due to the increase of fibrosis of the arterial wall over time;[3-5]

- ANP is released during exercise. A stronger release predicts a better chance of staying in normal sinus rhythm (NSR);[6]
- ANP inhibits the excretion of cortisol, DHEA and aldosterone in a dose-dependent manner;[7]
- ANP may possess anti-inflammatory properties;[8]
- ANP levels are higher during an afib episode than during NSR;[3]
- ANP levels are higher when laying on the right side (right lateral decubitus position);[9]
- A higher ANP level predicts a quicker return to NSR from an episode;[3]
- ANP blocks the calcium channels in cardiac myocytes;[10]
- ANP suppresses the RAAS.[11]

ANP has been synthesized and is available as the drug carperitide, which is used in the treatment of congestive heart failure.

Brain natriuretic peptide (BNP) acts very similar to ANP with the following actions being of particular importance:

- BNP causes the excretion of sodium and water via the kidneys and urine;[12]
- BNP suppresses the RAAS, lowers aldosterone level, and inhibits the release of norepinephrine and other catecholamines.[13,14]

BNP has been synthesized and is available as a drug called nesiritide. This drug has the same effects as BNP itself. It has no effect on potassium levels nor does it cause arrhythmias.[14-16]

RAAS

The renin-angiotensin-aldosterone system is the body's main system for dealing with a decrease in blood pressure that is too great to be handled by the autonomic nervous system alone. The primary purpose of the RAAS is thus to increase blood pressure by preserving (hoarding) sodium and water. The RAAS is normally activated by hypotension caused, for example, by a sudden shift from supine to standing position. The low blood pressure is first sensed by the kidneys, which proceed to secrete a small peptide called renin. Renin is transported to the liver where it helps to produce angiotensin I from a large protein called angiotensinogen. Angiotensin I, in turn, is carried by the blood to the lungs where it is converted into angiotensin II.

Angiotensin II (inhibited by ACE inhibitors) is the most potent vasoconstrictor in the body. It causes the blood vessels to constrict and potentiates the sympathetic nervous system resulting in an increase in blood pressure. Angiotensin II also acts on the adrenal glands to produce the hormone aldosterone. Aldosterone causes sodium and water to be retained by the kidneys thus increasing the body's fluid content and thereby the blood pressure. The action of the renin-angiotensin part of the RAAS may take seconds to minutes to kick in, but it may take days or even weeks before the full effect of the steroid hormone aldosterone is felt.[17-19]

Aldosterone

Aldosterone is a so-called mineralocorticoid. The term "mineralo" refers to the fact that it deals with the metabolism or regulation of the mineral sodium. The term "corticoid" refers to the fact that it is produced in the cortex (outer part) of the adrenal glands (zona glomerulosa). The raw material for aldosterone is progesterone derived from cholesterol.

For many years it was thought that aldosterone only acted on the kidneys (distal renal tubule) and that its main role was to increase the sodium concentration in extracellular fluid so as to increase blood pressure. It is now clear that aldosterone receptors are found in many other parts of the body including the brain, heart, blood vessels and intestines. As a matter of fact, the highest concentration is found in the hippocampus region of the brain.[20]

A flood of recent research findings has made it abundantly clear that aldosterone is a very bad actor indeed when it comes to heart health. It has been implicated in congestive heart failure, sudden cardiac death, stroke, and endothelial dysfunction. The belief is that aldosterone exerts its negative effects through the following mechanisms[20]:

- Inflammation and fibrosis (tissue scarring and thickening);
- Increased tendency to blood clotting;
- Impaired fibrinolysis (impaired blood clot digestion and removal);
- Sodium retention;
- Potassium and magnesium loss;
- Disturbance of ANS balance;
- Increased activity of catecholamines (norepinephrine and epinephrine);
- Decreased heart rate variability;
- Increased production of reactive oxygen species (ROS), especially superoxide;
- Decreased production of nitric oxide (NO) and accompanying endothelial dysfunction.

Although aldosterone production is primarily initiated by activation of the RAAS, it can also be initiated by ACTH, the same hormone that stimulates the secretion of cortisol[18]. A high potassium level or a low sodium level also causes aldosterone secretion to be increased[2,20]. A magnesium deficiency causes an increase in aldosterone production and subsequent hypokalemia (potassium deficiency)[21,22]. An excess of calcium ions (Ca⁺⁺) can also increase aldosterone production because excess Ca⁺⁺ increases the secretion of ACTH[23]. DHA (docosahexaenoic acid), a component of fish oil and GLA (gamma-linolenic acid) both inhibit the production of aldosterone[24].

An excessive production of aldosterone is involved in the disorder aldosteronism, which results in a constant overload of sodium and water as well as a deficiency in potassium. Aldosteronism can be caused by a benign tumour (adenoma) on the adrenal gland or simply by an enlargement (hyperplasia) of the adrenal gland. Hyperplasia itself has been linked to prolonged exposure to stress. Adrenal tumours are fairly common and can be genetically “ordained”. [25-28]

As discussed earlier, aldosterone must bind to a mineralocorticoid receptor (MC-receptor) before it can exert its effects. Although there is no question that too much aldosterone acting on receptors in the kidneys will lead to hypertension (high blood pressure), there is evidence that aldosterone can cause fibrosis in the heart muscle without accompanying hypertension[20]. Thus it would seem that aldosterone might have different effects depending on the location of the receptor that it happens to “dock” at.

Just to complicate matters further, it is also possible that a hormone with a molecular structure very similar to that of aldosterone could dock at the MC-receptors and thereby evoke exactly the same response as if aldosterone had docked there. One hormone that can do exactly this is cortisol, one of the body’s main stress hormones.

Cortisol

The body has one basic response to all types of stress; it releases stress hormones. In the case of acute stress, adrenaline (epinephrine) is released giving rise to the so-called “fight or flight” reaction. In the case of chronic or long-term stress, the body releases cortisol or at least attempts to do so. There is some overlap as to which hormones are released when, but generally adrenaline is released in response to short-term (acute) stress while cortisol is released in response to long-term (chronic) stress. Exposure to stress increases both cortisol levels and PACs, but to the best of my knowledge a cause and effect relationship between the two has not been established. There is also evidence that cortisol levels are elevated during a LAF episode[29].

As discussed earlier, the release of cortisol is initiated in the hypothalamus region of the brain. This region receives input concerning physical and psychological stressors acting on the body and, if they cannot be dealt with by the central or autonomic nervous system, the hypothalamus initiates the release of stress hormones. Corticotropin-releasing hormone (CRH) is produced in the hypothalamus in order to carry a message to the pituitary gland to produce and release adrenocorticotrophic hormone (ACTH) that, in turn, is carried in the blood stream to the outer part of the adrenal glands where the production of cortisol is initiated.

Cortisol is a so-called glucocorticoid. The term “gluco” refers to the fact that cortisol is involved in glucose regulation and the term “corticoid” refers to the fact that it is produced in the cortex (outer part) of the adrenal glands (zona fasciculata). The raw material for cortisol is progesterone derived from cholesterol.

The main role of cortisol is to increase glucose levels when needed. To accomplish this the hormone docks at glucocorticoid receptors thereby initiating the appropriate action. However, as discussed earlier, cortisol can also dock at MC-receptors and unleash an entirely different chain of events[30].

The circulating level of cortisol is about 1000-fold higher than the circulating level of aldosterone, so on the surface, it would seem that cortisol would be far more likely to dock with a MC-receptor than would aldosterone. Cortisol, however, is mostly bound to large protein carrier molecules so is not free to dock without further instruction. It is also fairly rapidly converted to cortisone, at least in the kidneys, and cortisone does not bind to the MC-receptors[30].

11-beta-hydroxysteroid dehydrogenase

The conversion of cortisol to cortisone is aided by the enzyme 11-beta-hydroxysteroid dehydrogenase type 2 (11-BHDT2), which also helps aldosterone achieve preferential binding to its receptors. 11-BHDT2 is thus crucial in ensuring that aldosterone rather than cortisol docks at the MC-receptors. If 11-BHDT2 is inhibited in any way then cortisol can gain the upper hand and initiate the aldosterone effects, including hypokalemia, in the absence of aldosterone[31-35].

11-BHDT2 is inhibited by a component in licorice (glycyrrhizic acid) and a deficiency of 11-BHDT2 can also occur due to a genetic defect[26,32,35]. Although no other inhibitors (chemical, environmental or psychological) of 11-BHDT2 are currently known it would seem odd that glycyrrhizic acid should be the only one[36]. Hopefully, future research will shed further light on this.

Aldosterone and LAF

Although aldosterone has been linked to ventricular arrhythmias there is, as far as I know, no published medical evidence to the effect that it is associated with LAF. Could there be an association?

- Inflammation and fibrosis of the heart tissue are found in most LAF patients[37,38]. Aldosterone causes inflammation and fibrosis of the heart tissue by direct action on the MC-receptors in the myocardium. This action is not accompanied by hypertension[2,20].
- Most LAF patients suffer from a systemic inflammation as expressed in abnormally high CRP (C-reactive protein) levels[39,40]. Aldosterone causes inflammation[2,20].
- Atrial fibrillation is associated with an increased level of reactive oxygen species (ROS) in the heart tissue[41,42]. Aldosterone causes an increased level[20].
- Atrial fibrillation is associated with an imbalance in the ANS. Aldosterone causes an imbalance, primarily by increasing sympathetic activity[2,20].
- A lack of nitric oxide (NO) in the myocardium, particularly the left atrial appendage, has been implicated as a major cause of stroke in atrial fibrillation[43,44]. Aldosterone inhibits the production of NO in the myocardium[20].
- Hypokalemia (low potassium levels) is associated with an increase in PACs, which in turn are associated with an increased risk of LAF episodes. Aldosterone promotes hypokalemia[20].
- Hypomagnesemia (low magnesium levels) is associated with an increase in PACs, which in turn are associated with an increased risk of LAF episodes[45]. Aldosterone promotes hypomagnesemia[20].

I would certainly seem that an elevated aldosterone level could well be the villain in the LAF story. However, it should be kept firmly in mind that it is not really the aldosterone level as such that is important, but rather the number of MC-receptors that are being activated. This activation, as we know, can be initiated not only by

aldosterone, but also by cortisol. If cortisol levels are abnormally high or the 11-BHDT2-aided conversion to cortisone is inhibited then cortisol may actually be the main villain.

So, if aldosterone or cortisol is the main villain, could the natriuretic peptides be the heroes?

Natriuretic Peptides

Atrial and brain natriuretic peptides are released in copious amounts during a paroxysmal afib episode. Could this release be what ultimately helps terminate the episode?

- Aldosterone causes inflammation[2,20]. Atrial natriuretic peptide (ANP) has anti-inflammatory properties[8].
- Aldosterone causes an imbalance in the ANS by increasing sympathetic activity[2,20]. Brain natriuretic peptide (BNP) inhibits the release of norepinephrine thereby reducing sympathetic activity[13,14].
- Aldosterone increases sodium levels and decreases potassium levels[2,20]. ANP decreases sodium levels and increases potassium levels.

Of overriding importance, however, is the fact that ANP and BNP both inhibit not only the RAAS, but also the production of aldosterone while ANP also inhibits the excretion of cortisol in a dose-dependent manner[7,13,14].

In other words, ANP and BNP strongly counteract the effects of aldosterone and cortisol. So if aldosterone and/or cortisol are the villains then ANP and BNP could indeed be the heroes. This is all speculation on my part. To the best of my knowledge, there is no scientific evidence that aldosterone or cortisol initiates an afib episode or that ANP and BNP help terminate it. This could be because the hypothesis is invalid or because no one has seriously considered it before.

The Hypothesis

A possible scenario for the interplay between aldosterone and cortisol, on the one hand, and ANP and BNP, on the other, can perhaps best be visualized as a play in three acts.

Prologue

Everything is calm and serene. Cortisol levels are low, electrolytes are perfectly balanced, and PACs and PVCs are non-existent or at least few and far between – life is good!

Act I

Aldosterone and 11-BHDT2 (beta) are on center stage as the curtain opens. Aldosterone may have gotten there because of an adrenal adenoma, hyperplasia of the adrenal gland, perhaps caused by many years of excessive stress or it may just be there because of a serious magnesium deficiency or a calcium overload. Beta is there to help aldosterone do its job and to help convert cortisol to cortisone.

The presence of aldosterone diverts beta from its role in converting cortisol into its inactive metabolite cortisone. This causes cortisol (stress) levels to rise and PACs and PVCs to make their presence felt again. This effect will be magnified if beta levels are low or beta production is inhibited. The rising cortisol levels induce glucose and insulin production, which in turn encourages intracellular migration of potassium (K+) and subsequent hypokalemia.

In the meantime aldosterone does what it is supposed to do, that is, instruct the kidneys to hoard sodium (Na+) and water. The rising cortisol level, especially if accompanied by beta inhibition, will also result in increased binding to MC-receptors thus amplifying the negative effects of aldosterone.

The end result is a pronounced shift in Na+/K+ balance favouring Na+. Combine this with the increase in PACs accompanying the cortisol build-up and the stage is set for an afib episode. The situation becomes even more

"explosive" if a high carbohydrate diet is adhered to and is, of course, exacerbated if a genetic predisposition to LAF is present.

It is conceivable, but not proven that diet and lifestyle could affect the time it takes for aldosterone concentrations to build up to a "dangerous" level. Thus episodes might occur at regular intervals in a person with a very regular lifestyle and stress level and a fairly unvaried diet.

Act II

The frequency of PACs increases with rising stress (cortisol) levels. The autonomic nervous system (ANS) becomes increasingly frantic in trying to keep things under control, but eventually it is overwhelmed by some event (trigger) that initiates an afib episode. The ANS of an afibber is exceptionally sensitive (dysfunctional) and the episode may be initiated by an inappropriately exuberant response to a trigger from either the sympathetic (adrenergic) or parasympathetic branch of the ANS.

In the very early stage of an episode it may be possible to abort it by doing a Valsalva manoeuvre, taking a beta-blocker (adrenergic afibber) or antiarrhythmic drug or moving around (vagal afibber). However, within five minutes or so the ion channels in the cardiac myocytes are likely to have been altered to the point where these approaches are no longer effective. At this point the ANS is basically out of the loop and the heart is left with its uncontrollable, chaotic beating.

It is still possible to terminate the episode by infusing a membrane-modifying drug (anti-arrhythmic) that will close down a sufficient number of sodium channels to bring the heart back into normal sinus rhythm. In other words, the effect of the drug is the same as what would be obtained by a sudden lowering of Na⁺ levels.

It is also possible to lower the heart rate by infusing or taking orally a calcium-channel blocker. The effect of this drug is similar to what would occur with a drop in Ca⁺⁺ concentration.

However, without pharmacological intervention, the afib episode will carry on until it terminates on its own.

Act III

The violent movement and stretching of the atria and ventricles caused by the fibrillation result in the release of ANP and BNP. These hormones immediately start dumping Na⁺ and water through the kidneys causing increased urination and normalizing the Na⁺/K⁺ ratio. ANP partially blocks the calcium channels in cardiac myocytes and thereby helps slow the heart rate. ANP also suppresses not only aldosterone and cortisol production, but the entire RAAS causing aldosterone to leave the stage. This frees up beta to concentrate on converting cortisol to inactive cortisone resulting in a normalization of cortisol levels.

Once the Na⁺/K⁺ ratio and cortisol levels have been normalized the factors sustaining the afib have been removed and the ANS will once again be able to take control and terminate the episode. The return to normal sinus rhythm can sometimes be facilitated by light exercise, which is known to release additional ANP.

The duration of the afib episode will depend on the vigour of the ANP response. This response is less pronounced in older afibbers and in afibbers with LAF of long standing because of the progressive fibrosis of the heart tissue caused by many episodes.

Epilogue

Everything is calm and serene. Cortisol levels are low, electrolytes are perfectly balanced, and PACs and PVCs are non-existent or at least few and far between – life is good!

AND THEN THE CYCLE STARTS ALL OVER AGAIN!!

Additional Musings

Fibrosis of the heart tissue occurs through direct binding of aldosterone to MC-receptors in the myocardium and is not accompanied by hypertension. Thus it is possible that the whole scenario may play out in the heart and that the kidneys are only marginally involved.

It is also conceivable that abnormal aldosterone levels are not involved at all. High cortisol levels, especially in conjunction with beta inhibition, could cause the same end result through binding to the MC-receptors. Both adrenergic and vagal afibbers tend to have high cortisol levels because of hypersensitivity to emotional stress and exposure to excessive exercise respectively.

It may be possible to verify or negate the presence of abnormally high aldosterone levels as a cause of LAF by measuring the levels immediately before and after an episode. The presence of aldosteronism can be determined by measuring plasma aldosterone-renin ratio.

Alternatively, is it possible that LAF is a form of subclinical aldosteroidism or – far out – that LAF is actually the body's first line of defence against the development of permanent hypertension?

Implications for Management of LAF

The hypothesis, and please keep in mind that this is all it is, would suggest several approaches to improving the management of LAF.

It is clear and supported by the analysis of the diets of afibbers who have “kicked the habit” that a high magnesium and potassium intake combined with a low intake of sodium and calcium are essential factors in preventing afib episodes.

Magnesium deficiency is widespread and both magnesium and potassium are highly effective in preventing PACs, the forerunners of a full-blown afib episode.

High carbohydrate meals with their resulting insulin release and hypokalemia should clearly be avoided. An overly exuberant insulin release can also be avoided by ensuring that each meal and snack contains some protein.

One of the LAF surveys found that vagal afibbers who supplemented with calcium had significantly more LAF episodes than vagal afibbers not supplementing. There was also a trend for all paroxysmal afibbers to have longer lasting episodes if they supplemented with calcium[46]. Calcium overload is a known cause of arrhythmia.

Large doses of vitamin C, phosphatidylserine and Moducare (sterols and sterolins) have all been found to be effective in helping to keep cortisol levels under control[47-49]. Could they be effective in preventing LAF episodes?

DHA (docosahexaenoic acid) and GLA (gamma-linolenic acid) inhibit the production of aldosterone. Could they be effective in preventing episodes?

Sustained, vigorous exercise (more than about 40 minutes) sharply elevates cortisol levels. Could going easy on exercise help prevent afib episodes?[50-51]

Neseritide (synthetic BNP) or carpetitide (synthetic ANP) may prove useful in terminating episodes and would almost certainly have fewer side effects than currently used antiarrhythmics.

Spironolactone, a potassium-sparing diuretic, is highly effective in blocking MC-receptors. By doing so, it rebalances the ANS (increase parasympathetic activity and decreases sympathetic activity), decreases the risk

of stroke, prevents hypokalemia, reduces fibrosis, improves endothelial function, and helps prevent hypertension (by blocking MC-receptors in the brain)[1,20]. Could spironolactone help extend the period between LAF episodes or prevent them altogether? Clearly it is a possibility, but one that only a clinical trial can confirm or deny.

Spironolactone, unfortunately, has several nasty side effects, especially breast enlargement and impotence. It is therefore not likely to be a viable long-term solution for LAF prevention. However, a “cousin” of spironolactone, eplerenone, has recently been developed and shows great promise in initial trials. Eplerenone is significantly more effective than spironolactone and animal experiments have shown that it protects the heart, brain and kidneys, especially against stroke and vascular injury[1,20]. Eplerenone does not cause breast enlargement or impotence. Could this new drug help prevent episodes? If the hypothesis is correct, it is certainly a very real possibility, but of course only a clinical trial will tell.

Conclusion

The on/off nature of paroxysmal atrial fibrillation and the experiences of many afibbers point to a hormonal connection. It is clear that the production of natriuretic peptides ANP and BNP increases during an episode and it is possible, but by no means proven, that they may play a role in the termination of episodes. Thus if ANP and BNP are the “good” actors, is it possible that their “counter” hormones aldosterone and cortisol could be the “bad” actors? Clearly, a full-scale research effort will be required to prove or disprove this hypothesis. However, if the hypothesis, or a more suitable variant of it, is indeed correct, then a whole new concept, both dietary and pharmacological, opens up in the prevention and termination of atrial fibrillation episodes.

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AFIB News

Caffeine – good or bad for the heart?

ZURICH, SWITZERLAND. Swiss researchers have investigated the effect of caffeine and coffee on heart rate, blood pressure, and sympathetic nervous system activation. Their study involved 15 healthy volunteers (6 habitual and 9 non-habitual coffee drinkers). Heart rate, blood pressure and muscle sympathetic nervous activity (MSA) were recorded before and after drinking a triple espresso, a decaffeinated triple espresso or after intravenous injection of 250 mg caffeine or placebo.

Intravenous injection of caffeine increased MSA significantly (by about 54%) in both habitual and non-habitual coffee drinkers. Drinking a triple espresso also increased MSA by about 50% (1 hour after consuming the coffee) in both habitual and non-habitual coffee drinkers. There was also a marked increase in systolic and diastolic blood pressure (12.6 and 7.1 mm Hg respectively) in non-habitual coffee drinkers, but no significant changes were observed in habitual coffee drinkers.

The effects of decaffeinated coffee were particularly interesting. In non-habitual coffee drinkers ingestion of decaffeinated coffee caused an increase in systolic blood pressure of 12.3 mm Hg (after 1 hour) and an increase in MSA of 22%. Thus it is clear that a significant part of coffee's stimulating effect on the cardiovascular system is due, not to caffeine, but to some currently unknown other component. The Swiss researchers in a

related comment note that a full bladder tends to activate the sympathetic nervous system (so if you are an adrenergic or mixed afibber, don't delay your trip to the bathroom!).

In related research, a team of Australian and Dutch researchers reports that caffeine consumption increases blood pressure and significantly reduces parasympathetic (vagal) activity about 60 to 90 minutes after ingestion. Combining the results of the two studies show that coffee drinking significantly alters autonomic nervous system balance in favour of increased sympathetic activity and decreased parasympathetic activity.

Corti, R, et al. Coffee acutely increases sympathetic nerve activity and blood pressure independently of caffeine content. Circulation, Vol. 106, December 3, 2002, pp. 2935-40

Sondermeijer, HP, et al. Acute effects of caffeine on heart rate variability. American Journal of Cardiology, Vol. 90, October 15, 2002, pp. 906-07

Editor's comment: These recent findings confirm that consumption of coffee, even decaffeinated, is bad news for adrenergic afibbers and probably should be avoided by mixed afibbers. The situation is less clear when it comes to vagal afibbers. A cup of coffee (even decaffeinated?) with dinner may decrease vagal activity enough to prevent a postprandial episode; however, it is possible that there could be a rebound effect.

Nitric oxide and stroke

ATLANTA, GEORGIA. Nitric oxide (NO) is generated by nitric oxide synthase (NOS), which is formed in the endothelium (lining of the heart muscle) during normal operation of the heart. NO is known to inhibit platelet activation and in general,

prevent the formation of blood clots. It also inhibits the synthesis of plasminogen activator inhibitor-1 (PAI-1), a potent generator of blood clots. It is also well established that a prolonged atrial fibrillation

episode increases the risk of an ischemic stroke (a stroke caused by a blood clot).

Researchers at Emory University School of Medicine recently decided to investigate if there is any association between atrial fibrillation and NO production. They put 7 pigs into atrial fibrillation and compared their NO production (in the left atrium) with that of pigs in normal sinus rhythm (NSR). They found that NO production in the left atrium of fibrillating pigs was 73% lower than in the pigs in NSR and that the level of PAI-1 was 1.8 times higher. Both these changes would markedly increase the risk of blood clotting and subsequent stroke. The researchers also noted that the abnormalities were not detectable until about 12 hours after the onset of the afib episode and increased progressively with the duration of the episode. They conclude that this may be the reason why the risk of stroke is low with afib episodes lasting less than 1 or 2 days.

In an accompanying editorial, researchers at the Krannert Institute of Cardiology point out several other important functions of NO production in the left atrium. Among them a reduction in sympathetic and an increase in parasympathetic activity and a reduction in calcium overload induced remodelling of the heart's electrical system.

Cai, H, et al. Downregulation of endocardial nitric oxide synthase expression and nitric oxide production in atrial fibrillation. Circulation, Vol. 106, November 26, 2002, pp. 2854-58

Rubart, M and Zipes, DP. NO hope for patients with atrial fibrillation. Circulation, Vol. 106, November 26, 2002, pp. 2764-66

Editor's comment: The finding that NO production helps prevent blood clotting and is decreased in the left atrium during fibrillation ties in with recent findings that aldosterone increases the level of superoxide, which in turn inhibits NO activity.

THE AFIB REPORT is published monthly by:
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E-mail: editor@afibbers.org World Wide Web: <http://www.afibbers.org>
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