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REVIEW

Heart rate variability in atrial fibrillation: the balance between sympathetic and parasympathetic nervous system

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Abstract

Background: Atrial fibrillation (AF) is the commonest abnormal heart rhythm with significant related morbidity and mortality. Several pathophysiologic mechanisms have been advocated to explain the onset of AF. There has been increasing evidence that abnormalities of the autonomic nervous system (ANS) that includes sympathetic, parasympathetic and intrinsic neural network are involved in the pathogenesis of AF. This review will consider the anatomical and pathophysiological concepts of the cardiac neuronal network and discuss how it can be investigated.

Design: Relevant articles for this review were selected primarily from Ovid Medline and Embase databases. We searched for key terms 'atrial fibrillation', 'AF', 'autonomic dysfunction' 'autonomic nervous system' 'heart rate variability' and 'HRV' to gather relevant studies. Duplicate papers were excluded.

Results: Heart is richly innervated by autonomic nerves. Both sympathetic and parasympathetic system interact in developing AF along with cardiac ganglionated plexi (GP). Thus autonomic dysfunction is present in AF. There are methods including selective ablation that reduce autonomic innervation and show to reduce the incidence of spontaneous or induced atrial arrhythmias. Heart rate variability (HRV) is a useful tool to assess sympathetic and parasympathetic influences on disease states. HRV can be improved following intervention and is thus a useful application in assessing autonomic dysfunction in patients with AF.

Conclusion: ANS plays a crucial role in the development, propagation and complexity of AF. Assessment of the autonomic involvement in the propagation of AF may help in explaining why certain patients with AF do not benefit from cardioversion or ablation.

Keywords: Autonomic nervous system; heart rate; autonomic dysfunction; vagal tone; atrial fibrillation

Introduction

Atrial fibrillation (AF) is the commonest abnormal heart rhythm with significant related morbidity and mortality. From the general population, 1-2% is affected by AF, however the prevalence of this condition rises to approximately 10% in individuals aged > 75 years.[1-3] There were 8.8 million adults with established AF in 2010 in Europe and this is expected to increase to 17.9 million by 2060.[3] AF is an independent risk factor for stroke.[4] It is associated with a 5-fold increase in the risk of stroke, a 3-fold increase in the risk of heart failure and a 2-fold increase in the risk of death.[1, 5]

Several pathophysiologic mechanisms (such as neurohormonal activation, structural changes, fibrosis, atherosclerosis, etc.) have been advocated to explain the onset of AF.[6] There has been increasing evidence that abnormalities of the autonomic nervous system (ANS) that includes sympathetic, parasympathetic and intrinsic neural network are involved in the pathogenesis of AF.[7] This review will consider the anatomical and pathophysiological concepts of the cardiac neuronal network and discuss how it can be investigated.

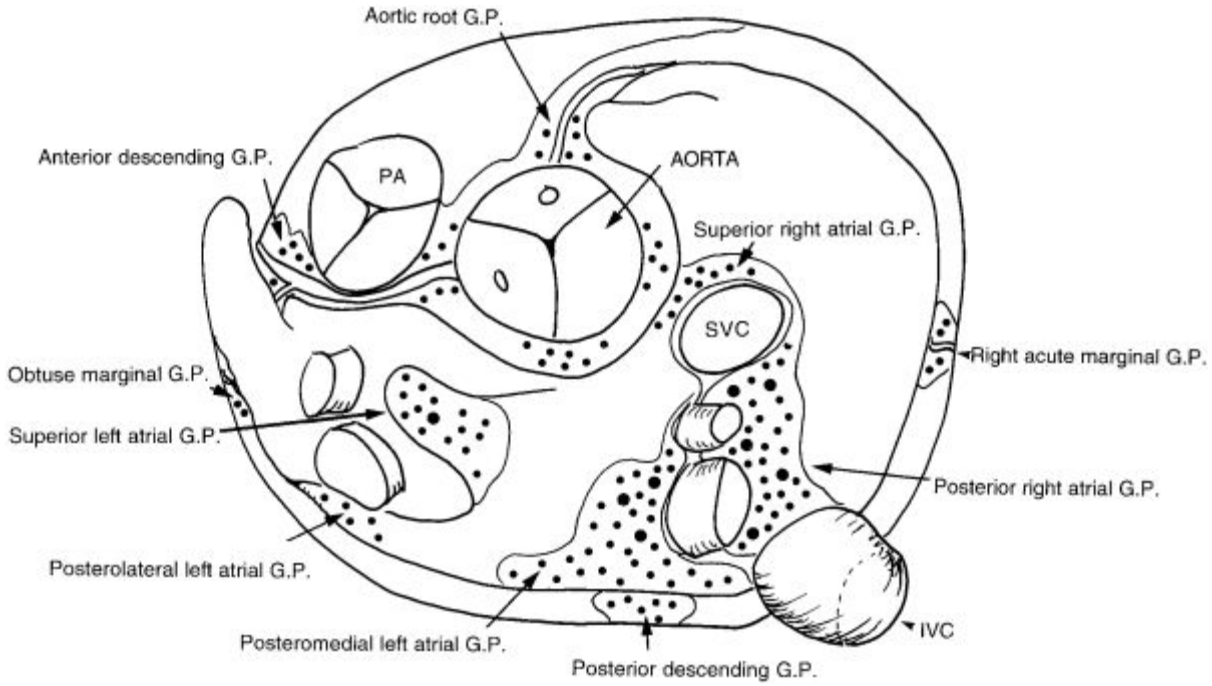
Anatomy of the cardiac autonomic nervous system

The heart is richly innervated by the autonomic nerves. The ANS of the heart consists of intrinsic and extrinsic ganglia.[8] The parasympathetic components of the extrinsic cardiac nervous system originate in the vagus nerve. The extrinsic sympathetic innervation is mediated via the cervical, stellate (cervicothoracic), and thoracic ganglia. Interestingly, vagus nerve also contains sympathetic fibres and conversely, parasympathetic fibres are also found in sympathetic nerves.[9-11]

Baroreceptors, chemoreceptors and mechanical stress receptors located in the heart and great vessels regulate autonomic tone.[8] Moreover, clusters of intrinsic ganglia form a complex neural network composed of ganglionated plexi (GP), which are situated in the atria in multiple locations and attenuate the interactions between the extrinsic and intrinsic nervous systems (see figure 1).[12] GP are suitably innervated with both adrenergic and vagal nerve endings and are situated in fat pads, close to the pulmonary vein ostia. The cardiac neural control occurs at

several levels with each level capable of parallel processing of afferent neurotransmission and efferent cardiac sympathetic outflow.[13]

Figure 1 – Cross sectional drawing of the heart showing the anatomical position of Ganglionated plexi (GP) (image obtained from Armour *et al* with permission)[14]



G.P = Ganglionated plexus, PA = Pulmonary artery, SVC = Superior vena cava, IVC = Inferior vena cava.

Autonomic dysfunction in atrial fibrillation

There has been detailed exploration into the autonomic mechanisms underlying AF. Scherf and colleagues first proposed the theory of focal firing based on their observations that rapid firing of action potentials and/or AF occurred following application of either acetylcholine (ACh) or aconitine and it terminated once the source was removed by cooling.[15, 16] Studies by Moe *et al* further demonstrated that AF could be initiated by premature beats during stimulation of the vagus nerve.[17] Other basic science studies also showed that electrical stimulation of autonomic nerves innervating the heart could induce AF.[18, 19]

Sympathetic system promote arrhythmia by increasing calcium transient in the synapses.[20] Calcium entry into the presynaptic neuron through voltage gated calcium channels is essential for neurotransmitter release. Activated β-adrenergic signal pathways increase calcium entry into the presynaptic neuron and the spontaneous release of calcium from sarcoplasmic reticulum.[20] This leads to neurotransmitter release and thus increase in action potential frequency.

On the other hand, vagal stimulation contributes to development of AF by heterogenous shortening of action potential duration and refractory period.[7] ACh activates the muscarinic receptors (mainly M2 in the heart). This in turn modulate cardiac ionic channels through direct activation of I_{KACh} (inward-rectifying potassium channel). I_{KACh} is a G protein-gated ion channel found in the sinoatrial node and atria and contributes to the regulation of heart rate by accelerating repolarisation and leading to hyperpolarisation. It also exerts its effect through indirect regulation by modulation of cyclic adenosine monophosphate (cAMP) mediated responses, a second messenger used for intracellular signal transduction (such as transferring into cells the effects of hormones like glucagon and adrenaline, which cannot pass through the plasma membrane).[21, 22] The overall result is shortening of action potential duration leading to AF.

Vagal stimulation has also been shown to cause conduction delays.[23, 24] Additionally, recent studies have shown evidence of noncholinergic vagal effects that may also contribute to the pathogenesis of vagally induced AF.[25, 26] These effects may be mediated by vagally released

polypeptide and vasoactive intestinal polypeptide (VIP), which enhance the delayed rectifier potassium current (I_{Ks}) and decrease sodium current and thus contribute to the vagal effects on atrial action potential duration and conduction velocities as well as increased propensity to AF.[7]

It has been demonstrated that there is significant vagal innervation of the atrial muscle sleeves extending into the pulmonary veins and other thoracic veins.[27] In normal heart, vagal influences are predominant, thus explaining that the clinical manifestation of vagal-mediated paroxysmal AF is preferentially seen in young male adults with absence of detectable heart disease.[28] Their electrocardiogram (ECG) pattern is of common flutter alternating with fibrillation.[28] Vagally mediated AF occurs more commonly in men than in women, and the onset of first episode is around 30 – 50 years of age.[28] Sympathetically mediated AF is less common and observed in the presence of any heart disease, the first effect of which is to induce vagal withdrawal.[28]

The anatomical distribution of the autonomic fibres is different for sympathetic and vagal innervation.[28] Sympathetic and parasympathetic terminals lie in close proximity to one another, and both are close to the target cells, yet do not have an identical distribution.[28] Thus stimulation of one system may affect function of the other.[28] For example, noradrenaline release from sympathetic nerves is diminished by the acetylcholine released from neighbouring vagal nerves.[28] Furthermore, the latency time and duration of the physiological response of each sympathetic and parasympathetic also differs.[28] The functional response to cholinergic stimulation occur within a few milliseconds whereas adrenergic stimulation requires seconds for target activastion.[28] This combination of inhomogeneity of the autonomic effects in space and time contributes to the difficulty in managing AF.

Previously, it was considered that sympathetic nervous system (SNS) drove most of exercise-induced AF; however Coumel and colleagues describe that electrophysiological characteristics of atrial cells (including action potential duration and refractoriness, conduction speed) are modulated differently by sympathetic and vagal influences.[28] The former tends to favour abnormal automaticity and triggered activity whereas the latter tends to influence macro re-entry phenomena.[28]

Other studies have shown that both sympathetic and parasympathetic system interact in developing AF.[29, 30] Additionally, cardiac GP may play a vital role in the pathogenesis of AF.[7] Clinically, the sites of ablation during PV isolation are often adjacent to the locations of GPs and PV isolation could lead to vagal denervation of the left atrium. Platt and colleagues were the first to describe that ablation of GPs may aid in terminating AF.[31] This was further supported by other studies, demonstrating the feasibility of selectively targeting GPs to suppress AF.[7, 32] Katritsis *et al* concluded that combination of PV isolation and GP ablation has higher success in suppressing AF when compared to PV isolation alone.[33]

There is evidence to support that in addition to the atrial remodelling that takes place in patients with AF leading to 'AF begets AF' hypothesis; there is structural remodelling (apoptosis and scaring) and autonomic remodelling, all of which promote the propensity and prolongation of AF episodes.[34, 35] The exact extent and mechanism(s) of such neural remodelling remain elusive. It is clear that autonomic dysfunction plays an important role in the pathogenesis of AF. There are methods that reduce autonomic innervation and thus show to reduce the incidence of spontaneous or induced atrial arrhythmias.[36-40] This suggests that neuromodulation may be helpful in controlling AF. Studies looking at altering of the sympathetic limb of ANS showed that suppression of sympathetic tone leads to a notable reduction in atrial vulnerability to AF induction and post-ablation AF recurrence.[41, 42]

Role of heart rate variability

Exploring the ANS is possible through heart rate variability (HRV) evaluation. It is well established that short-term, respiratory related variation of cardiac cycle reflects vagal activity, whereas variation over prolonged periods reflect neurogenic and humoral modulation of the sympathetic tone.[43] HRV is a non-invasive method to evaluate ANS activity and reflects the best ANS influence on heart rate.[44-46] HRV is a measure which indicates the variation in the heartbeat within a specific time frame. It is measured by looking at the heart rate that changes over time against the average heart rate, and is expressed as time and spectrum analytical methods.[47] It analyses variation in the beat to beat intervals of the heart and reflects the parasympathetic nervous system (PNS) and SNS balance.[48] Variations in heart rate may be evaluated by a number of

methods but the commonly used methods in HRV are time domain and frequency domain. The most commonly used measures of each domain are presented in table 1.

Time domain indices of HRV quantify the amount of variability in measurements of the interbeat interval (IBI), which is the time period between successive heartbeats.[48] Some of the common time domain metrics include SDNN, SDNN Index (SDNNI), RMSSD, NN50 and pNN50. Briefly, SDNN is the sum contribution of both SNS and PNS. It is more accurate when calculated over 24 hours than during shorter periods and is the gold standard for medical stratification of cardiac risk when recorded over a 24 hour period.[43] SDNN values predict both morbidity and mortality. Based on 24 hour recording, patients with SDNN values below 50 ms are classified as unhealthy, 50 – 100 ms have compromised health, and above 100 ms are healthy.[49]

SDANNI reflects autonomic influence on HRV and correlates with VLF power over a 24 hour period. RMSSD reflects the beat-to-beat variance in HR and is the primary time-domain measure used to estimate the vagally mediated changes reflected in HRV.[50] 24 hour RMSSD measurements strongly correlate with pNN50 and HF power.[51] The RMSSD is more influenced by the PNS than SDNN. Lower RMSSD values correlate with high risk of sudden unexplained death in epilepsy.[52]

Frequency domain measurements are analogous to the electroencephalogram (EEG) where autoregressive modelling is used to separate HRV into its component ULF, VLF, LF and HF rhythms that operate within different frequency ranges. This concept is similar to a prism that reflects light into its component wavelengths.[43] It includes ULF, VLF, LF, HF and LF/HF ratio. Briefly, ULF correlates highly with SDANN time-domain index and represents very slow-acting biological processes, core body temperature, metabolism and the renin-angiotensin system. VLF is more strongly associated with all cause mortality than LF or HF. Low VLF power has been associated with arrhythmic death, post traumatic stress disorder (PTSD), high inflammation, low levels of testosterone, heart's intrinsic nervous system, physical activity, thermoregulatory, renin-angiotensin and endothelial influences on the heart.[50, 53-59] PNS activity may contribute to VLF power since parasympathetic blockade almost completely abolishes it whereas SNS does not influence VLF power.[43, 60]

In contrast, LF power is produced by both PNS and SNS as well as blood pressure regulation via baroreceptors.[43, 58, 61] However, PNS is predominant in LF. Respiratory-related efferent vagally mediated influences are particularly present in the LF band, for example when taking a deep breath or sigh.[62] The HF band reflects parasympathetic activity and is also referred to as the respiratory band as it corresponds to the heart rate variations related to the respiratory cycle. HF power is highly correlated with the pNN50 and RMSSD time-domain measures.[63] HF power may increase at night and decrease during the day.[64] Lower HF power is related to stress, panic or anxiety.

It is believed that an increase of the PNS tone increases HRV while a vagal withdrawal may reduce HRV.[44-46, 65] Low HRV is indicative of reduced cardiac parasympathetic function and is associated with worse cardiovascular outcomes.[53, 66] In sinus rhythm, high HRV signifies a good cardiovascular adaptive response to various endogenous and exogenous factors.[47] HRV is found to be lower in several cardiac and non cardiac disease states including coronary artery disease, congestive heart failure, hypertension, rheumatoid arthritis, aging and diabetic neuropathy amongst other.[49, 53, 66-68] In the absence of direct intraneural recordings of cardiac autonomic activity in humans, HRV analysis has provided a useful indirect surrogate.[69]

AF is characterised by marked HRV. The patterns of atrial excitation in AF, the conduction properties of the atrioventricular node and the modulating effects of the ANS appear to be influential.[70-73] HRV has been studied extensively in patients with normal sinus rhythm and shown to have important prognostic implications for various cardiovascular disorders (see table 2).[44, 49, 53, 74, 75] However, there have been relatively few published reports dealing with the phenomenon in AF.[73, 76, 77] A study by Friedman showed that increasing left atrial size was associated with less HRV, suggesting a role of the left atrium in modulating the cardiovascular effects of the ANS.[78] Other studies have shown use of HRV in AF and described that HRV indices correlate well with vagal tone.[47, 73] They concluded that HRV in patients with AF is related to vagal tone.[47, 73] HRV is thus a useful way of assessing autonomic dysfunction in patients with AF.

Conclusion

The evidence shows that ANS plays a crucial role in the development, propagation and complexity of AF. The mechanisms underlying the process of autonomic dysfunction within the myocardium are intricate and perhaps, this explains why this concept has not received enough recognition. Assessment of the autonomic involvement in the propagation of AF may help in explaining why certain patients with AF do not benefit from cardioversion or ablation. The advent of non invasive techniques, such as heart rate variability has allowed to assess the role of ANS in AF in greater detail. There is further data to support that modulation of the ANS is possible and prudent. This may prove to be a useful addition in the management of AF along with existing therapy.

Disclosures

AAK has no financial interest in the subject matter or materials discussed.
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Table 1 – Common time domain and frequency domain measures of HRV (adapted from Malik *et al*)[48]

Variable	Units	Description
Time domain measures		
NN interval	ms	Normal to normal interval
SDNN	ms	Standard deviation of all NN intervals.
SDANN	ms	Standard deviation of the averages of NN intervals in all 5 min segments of the entire recording.
RMSSD	ms	The square root of the mean of the sum of the squares of differences between adjacent NN intervals.
SDNN index	ms	Mean of the standard deviations of all NN intervals for all 5 min segments of the entire recording.
SDSD	ms	Standard deviation of differences between adjacent NN intervals.
NN50 count	ms	Number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording. Three variants are possible, counting all such NN intervals pairs or only pairs in which the first or the second interval is longer.
pNN50	%	NN50 count divided by the total number of all NN intervals.
Frequency domain measures		
5 min total power	ms^2	The variance of NN intervals over the temporal segment [Frequency range: $\leq$ 0.4 Hz]
ULF	ms^2	Power in the ultra low frequency range [Frequency range: $\leq$ 0.003 Hz]
VLF	ms^2	Power in very low frequency range [Frequency range: $\leq$ 0.04 Hz]
LF	ms^2	Power in low frequency range [Frequency range: 0.04 – 0.15 Hz]
LF norm	n.u.	LF power in normalised units. LF/Total Power-VLF) x 100
HF	ms^2	Power in high frequency range [Frequency range: 0.15 – 0.4 Hz]
HF norm	n.u.	HF power in normalised units. HF/Total Power-VLF) x 100
LF/HF	ms^2/ ms^2	Ratio of low frequency range and high frequency range

Table 2 – Utility of HRV in cardiovascular disease states and risk factor conditions

Author(s)	Year	Condition studied	Number of patients	Summary
Abdelnabi *et al*[65]	2019	Coronary artery disease (CAD)	100	Complete revascularisation during coronary angiography associated with improved HRV (p<0.001).
Adlan *et al*[55]	2017	Rheumatoid arthritis	63	Time (RMSSD, pNN50%) and frequency (high frequency (HF) power, low frequency (LF) power, total power) domain measures of HRV were lower in the RA, RA-hypertension and hypertension groups compared to controls (p=0.001). High sensitivity CRP (hs-CRP) and pain were independently and inversely associated with time domain parameters of HRV.
Barauskiene *et al*[47]	2016	Atrial fibrillation (AF)	222	HRV significantly lower in AF patients (p<0.05). HRV was significantly higher in patients on betablockers than without (p<0.005).
Bigger *et al*[50]	1992	CAD	715	Each measure of HRV had a significant and at least moderately strong univariate association with all-cause mortality, cardiac death and arrhythmic death.
Frey *et al*[63]	1995	Heart failure (HF) and AF	35	SDANN was independently associated with survival on multivariate analysis. Dichotomized SDANN at 100 msec accurately predicted 12-month survival in 28 patients (relative risk = 9.77, p=0.001)

Friedman[64]	2004	AF	38	Reduced HRV correlated with increasing left atrial and left ventricular dimensions. Left atrial dimension is an independent determinant of HRV. HRV greater in lone AF than other cardiac disorders.
Kearney *et al*[61]	2002	HF	553	SDNN independent predictor of all-cause mortality. Hazard ratio (HR) of progressive HF death for a 10% decrease in SDNN was 1.06 (95% Confidence Interval (CI) 1.01-1.12).
Kleiger *et al*[54]	1987	CAD	808	SDNN had the strongest univariate correlation with mortality of all Holter variables. Relative risk of mortality was 5.3 times higher in the group with SDNN < 50ms than the group with SDNN > 100ms.
La Rovere *et al*[51]	1998	CAD	1284	SDNN < 70ms carried a significant multivariate risk of cardiac mortality (3.2 [95% CI 1.42-7.36])
Marinkovic *et al*[66]	2019	Paroxysmal AF (PAF)	100	HRV changes during the 3-month period after catheter ablation for PAF may predict long-term outcomes. SDNN cut-off value of 62.5 ms showed the best predictive ability for late recurrence AF (Area Under Curve (AUC) = 0.59 [95% CI 0.27-0.49], p = 0.04)
Mori *et al*[67]	2018	AF	54	Marked increase in HRV parameters observed immediately post cryoballoon ablation (CB) especially in patients who had left sided pulmonary vein (PV) isolation.

Rich *et al*[68]	1988	CAD	100	Decreased HRV and ejection fraction were the best predictors of mortality ($p<0.01$). HRV was an independent predictor of mortality.
Singh *et al*[52]	1998	Hypertension (HTN)	2042	HRV significantly lower in hypertensive men and women. LF associated with incident HTN in men (odds ratio (OR): 1.38; 95% CI 1.04-1.83 but not in women (OR: 1.12; 95% CI 0.86-1.46). Lower HRV associated with greater risk of developing HTN among normotensive men.
Stein *et al*[60]	1993	Mitral regurgitation (MR)	38	Heart rate, ultra low frequency (ULF), LF and LF/HF predicted mortality, progression to surgery and development of permanent AF. SDANN was an independent predictor of poor outcomes ($p=0.001$).
Stein *et al*[62]	1994	MR and AF	21	Reductions in measurements of ULF and HF were significant predictors of mortality or requirement for mitral valve surgery ($p=0.02$ and $p=0.05$ respectively).
van den Berg *et al*[59]	1997	AF	28	Baseline HRV was higher in AF group. After administration of methylatropine, HRV neared zero in the control group whereas it returned to baseline in AF group. SD, RMSSD, LF and HF at baseline were significantly ($p<0.05$) correlated with vagal tone in both groups. HRV in patients with AF related to vagal tone.
Zysko *et al*[69]	1999	CAD and PAF	68	No isolated stimulation of

				parasympathetic or sympathetic nervous system noted immediately prior to episode of PAF in patients with CAD. Cessation of PAF accompanied by increased RMSSD and pNN50.

Table 3 – Search strategy to look for articles containing atrial fibrillation and autonomic nervous system

	Searches	Results
1	atrial fibrillation.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy]	204025
2	af.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy]	129908
3	autonomic nervous system.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy]	121449
4	autonomic dysfunction.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy]	22430
5	1 or 2	262475
6	3 or 4	137164
7	5 and 6	2104

Table 4 – Search strategy to look for articles containing atrial fibrillation and heart rate variability

	Searches	Results
1	atrial fibrillation.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy]	204025
2	af.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy]	129908

3	heart rate variability.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy]	49842
4	HRV.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy]	26601
5	1 or 2	262475
6	3 or 4	54174
7	5 and 6	1448

Figure 2 – Flow diagram of process for identification of suitable studies to include in the review