

Do we need an individual approach to atrial fibrillation and adrenergic overload in the critically ill?

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ABSTRACT

Despite catecholamines being lifesaving drugs, they can also be harmful. Adrenergic overload is one of the major causes of supra- and ventricular arrhythmias, which induce haemodynamic instability of critically ill patients. In this paper we will focus on the pathophysiology of atrial fibrillation (AF), the importance of adrenergic overload for triggering AF, the importance of the autonomic nervous system and we will challenge the importance of decreasing adrenergic load with selective and non-selective β -blockers, which have different effects on the metabolism of the severely ill. We will also emphasize the importance of an individual approach due to pharmacogenetic differences in β -adrenergic signalling.

Key words: catecholamines, atrial fibrillation, beta-blockers, metabolism, resting energy expenditure

INTRODUCTION

Atrial fibrillation (AF) is a supraventricular tachycardia characterized electrically by chaotic atrial activation that results in mechanically ineffective atrial contraction. New-onset AF is a common arrhythmic complication of critical illness, with an incidence that varies from 4 to 9% in general intensive care unit patients, to 32 to 50% in patients after major cardiac and thoracic surgery. (1-2)

New-onset AF is associated with increased morbidity and mortality in patients hos-

pitalized for heart failure, as well as various other critical conditions, although it is possible that AF in these cases is primarily a marker of disease severity rather than a direct cause of death. (3,4)

AF is associated with cardioembolic events and heart failure, longer hospital stays, and reduced quality of life as well as a two to five-fold increased mortality. (5-6)

AF in critically ill patients can present as asymptomatic ECG changes or, on the other hand, it can cause severe hemodynamic instability with profound hypotension, myocardial ischemia and heart failure leading to pulmonary edema, cardiogenic shock, with subsequent tissue hypoxia and organ dysfunction. Highly symptomatic patients are candidates for synchronized electro-cardioversion. (7)

Despite catecholamines being lifesaving drugs, they can also be harmful. Adrenergic overload is one of the major causes of hemodynamic instability due to supra- and ventricular arrhythmias. In this paper we will focus on the pathophysiology of AF, the importance of adrenergic overload for triggering AF, the importance of the autonomic nervous system and in the end we will challenge the importance of decreasing adrenergic load. We will also emphasize the importance of an individual approach due to pharmacogenetic differences in β -adrenergic signaling. The catecholamines also have other non-cardiovascular effects, i.e. they have profound metabolic effects, elevating resting energy expenditure and changing substrate oxidation rates. Finally, we will discuss the possible pathways and effects of selective and

non-selective β -blockers on the hyper-metabolism of the severely ill.

PATHOPHYSIOLOGY OF AF

Structural and electrical atrial remodeling are fundamental mechanisms for AF. (8) The majority of critically ill patients have already acquired some structural and electrical atrial remodeling before intensive care unit (ICU) admission. Structural remodeling, particularly fibrosis, is the mainstay in many forms of AF. This fibrosis is primarily due to atrial dilatation, which leads to the local activation of the renin aldosterone angiotensin system (RAAS) and further initiates multiple cell signalling cascades, including inflammation and apoptosis, stimulating fibrosis, as well as possible modulation of ion channels and gap-junction dynamics. (9) Fibroblasts can couple electrically to cardiomyocytes and when increased in number, promote re-entry and/or ectopic activity. (10)

Electrical remodeling promotes AF by acting on the fundamental arrhythmia mechanism: focal ectopic activity and reentry. In this context, two principles gain attention: factors triggering the onset and factors perpetuating AF. (11)

Ectopic focal discharges often initiate AF. Rapidly firing foci initiating paroxysmal AF arise most commonly from the atrial myocardial sleeves that extend into pulmonary veins. (11) Although the pulmonary veins are the most common sites for ectopic focal triggers, they can also arise

elsewhere, including the posterior LA (left atrium), ligament of Marshall, coronary sinus, venae cavae, septum, and appendages. Atrial myocardial fibers are oriented in disparate directions, and possess unique anatomical and electrophysiological features for their arrhythmogenic nature. The relatively depolarized resting potentials in pulmonary vein myocytes promote sodium channel inactivation leading to abrupt changes in fiber orientation and thus favouring reentry. These myocytes also demonstrate abnormal automaticity and triggered activity that could promote rapid focal firing. (11)

The evolution of AF from paroxysmal to persistent to permanent forms through atrial remodeling can be caused by the arrhythmia itself and/or progression of underlying heart disease. Atrial electrical properties are modified by affecting expression and function of ion-channels, pumps, and exchangers, thus a reentry prone substrate is created which promotes arrhythmia. This concept is known as atrial remodeling and was first tested in animal models showing that long-term rapid atrial pacing or maintenance of AF favors the occurrence and maintenance of AF ('AF Begets AF'). (12) The developments of functional reentry substrates, which are reversible on AF termination, contribute to persistent AF.

There are more potential mechanisms for ectopic triggering. The resting potential of a normal atrial cell is maintained by high resting K⁺ permeability through the inward rectifier K⁺ current (IK1). Although normal human atrial cells also manifest pacemaker current (If), it is overwhelmed by much larger IK1, and does not manifest automaticity. Enhanced automaticity is caused by changes in this balance resulting from decreased (IK1) and/or enhanced (If). (13)

Early after depolarizations (EAD) involve abnormal secondary cell membrane depolarization during repolarization phases. EAD are caused mainly by action potential duration prolongation (i.e. congenital long QT-Syndrome). (14) This allows L-type Ca²⁺ current (ICaL) to recover from inactivation, leading to inward movement of Ca²⁺ ions causing EAD.

Delayed after depolarizations (DAD) are caused by abnormal diastolic release of Ca²⁺ from sarcoplasmic reticulum stores. Specialized sarcoplasmic reticulum Ca²⁺-channels (called ryanodine receptors

[RyRs]) release Ca²⁺ in response to transmembrane Ca²⁺ entry. (11) RyRs are normally closed during diastole but can open if they are functionally defective or if the sarcoplasmic reticulum is Ca²⁺ overloaded. When one Ca²⁺ ion is released during diastole, it is exchanged for three extracellular Na⁺ ions by the Na⁺-Ca²⁺ exchanger, causing a net depolarizing inward positive-ion movement (called transient inward current [Iti]) that underlies DADs. Congestive heart failure, one of the most common causes of AF, produces atrial cell Ca²⁺ overload and DADs. (15)

EFFECTS OF THE AUTONOMIC NERVOUS SYSTEM

Parasympathetic stimulation causes vagal discharge which enhances acetylcholine dependent K⁺ current (IKAch), reducing atrial action potential duration and refractoriness, increasing the susceptibility to reentry mechanism. (11) Sympathetic stimulation causes β-adrenoceptor (AR) activation, which increases diastolic Ca²⁺ leak and promotes DAD by hyperphosphorylating RyR2s, which promotes automaticity and triggered activity. Atrial sympathetic hyperinnervation occurs in persistent AF patients. (16) Autonomic neural remodeling contributes to positive feedback loops that promote AF persistence and recurrence. Plexi of autonomic ganglia that constitute the intrinsic cardiac autonomic nervous system are located in epicardial fat near the pulmonary vein-LA junctions, at the orifices of venae cavae in the right atrium and the ligament of Marshall. AF studies in critically ill patients after cardiac surgery have demonstrated that at least two routes of cardiac autonomic modulation pave the way to AF, (17-18) whereby a landmark study reported concomitant vagal withdrawal and sympathetic activation as a mode of perioperative AF activation. In sharp contrast, we have shown that patients developing AF after cardiac surgery, having had been on complete chronic beta blockade, exhibit different, parasympathetically (co)mediated routes of cardiac autonomic modulation with concomitant parasympathetic and excessive adrenergic activation. (19)

PROMOTORS OF AF IN CRITICALLY ILL PATIENTS

In critically ill patients with AF, we can detect and modify promoters of AF. (20) The most important promoter is adrenergic

overstimulation (i.e. stress, pain and inotropic support). Other important promoters are myocardial (atrial) stretch (i.e. fluid overload, acute mitral regurgitation, mitral stenosis, pulmonary embolism), inappropriate oxygen delivery to the myocardium (i.e. myocardial ischemia, hypovolemia, anemia), electrolyte disturbance (i.e. hypokalemia, hypomagnesemia), systemic and local inflammation (i.e. after on-pump cardiac surgery, sepsis, myo/pericarditis), hypothermia, concomitant increased vagal activity and intrinsic cardiac autonomous system hyperreactivity and endocrine disorders (i.e. hyperthyroidism, pheochromocytoma).

ADRENERGIC OVERLOAD

A recently published review explores the schizophrenic 'Jekyll-and-Hyde' characteristics of catecholamines in critical illness, as they are both necessary for survival yet detrimental in excess. (21) A hyperadrenergic state is responsible for the reversible myocardial depression seen in both phaeochromocytoma crisis (22) and the stress-related ("broken heart", Takotsubo) cardiomyopathy. (23) Adrenergic overstimulation is associated with a poor prognosis in acute coronary syndromes, heart failure, liver cirrhosis and acute cerebrovascular disease. (24-25)

Despite association with adverse outcomes, adrenergic agonists remain the cornerstone of cardiovascular support. Norepinephrine is the current recommended first-line agent for low vascular resistance states, while dobutamine is recommended for myocardial dysfunction. (26) Epinephrine has both inotropic and pressor properties that can be used as an alternative to either. (27) It is likely that these exogenous catecholamines will add further to the endogenous stress response, therefore increasing total adrenergic stress. (21) It was shown that dobutamine administration was independently associated with increased mortality in acute heart failure and after cardiac surgery. (28, 29) High levels of catecholamines as well as a persistently high heart rate predict poor patient outcomes in sepsis. (30,31) While high catecholamine levels could simply be a marker of disease severity, they may also be a perpetrator of further organ dysfunction. (21) Increasing catecholamine doses were associated with increasing mortality, independent of effects on blood pressure. (32)

One of the steps towards reducing adrenergic overload is to not necessarily target

“normal” or “supranormal” haemodynamic values. (21) While too low a blood pressure or cardiac output may compromise tissue perfusion and oxygenation, neither increasing blood pressure >65 mmHg (34) nor targeting “supranormal” values of cardiac output (34) translated into an overall survival benefit. Previously normotensive patients trended to worse outcomes when a higher blood pressure was targeted. (34) Unrecognized diastolic dysfunction may be also compromised further by the use of catecholamines. (35)

PHARMACOGENETICS

In some patients, inappropriate high ventricular rate is noticed despite relatively low inotropic or vasopressor dose after adequate volume resuscitation.

Pharmacogenetics can provide an answer to this diversity. (36) Twelve single-nucleotide polymorphisms have been identified in the β 1-AR, but only two of these are thought to be clinically relevant. At position 389, the glycine nucleotide in the G-protein coupling domain can be substituted for arginine. (37) This is again of function polymorphism, resulting in increased adenylate cyclase activity. The Arg/Arg genotype is associated with increased sensitivity of the β 1-AR to noradrenaline, (38) a 3- to 4-fold increase in signal transduction and an increase in the number of constitutionally active receptors compared with the Arg/Gly or Gly/Gly genotypes. (39) The other important β 1-AR polymorphism is at position 49 and is thought to have a modulating role in adenylate cyclase activity. (39) The gain of function Arg/Arg polymorphism is important because higher adrenergic activity has been shown to increase the likelihood of AF induction in a dose-dependent manner. (40) Bucindolol, a competitive antagonist of the β 1-AR, facilitates the inactivation of constitutionally active receptors (inverse agonism), and decreases levels of noradrenaline. (43) Bucindolol prevented new-onset AF in patients with heart failure with reduced ejection fraction in 74% of patients with the Arg/Arg genotype, but had no effect in those patients with the Gly/Gly genotype. (41) The substudy found that all-cause and cardiovascular mortality, as well as cardiovascular and heart failure hospitalizations were significantly reduced in patients with the Arg/Arg genotype, but not glycine carriers. (42) The enhanced adrenergic signaling in the Arg/ Arg genotype may render it more susceptible to β blocking drugs

sympatholytic actions, thereby preventing the induction of AF that might normally occur in these patients. Interestingly, the loss of function glycine 389 polymorphism is associated with a significantly better response to rate-controlling therapies in patients with AF. (43) This may be explained because the rate-control therapies can work synergistically with the attenuated β 1-adrenergic cascade caused by this genotype.

β 1-AR polymorphisms could also influence the efficacy of amiodarone because it possesses antiadrenergic effects. (44)

B-ANTAGONISTS AND DECATECHOLAMINIZATION IN CRITICALLY ILL PATIENTS

According to current guidelines, β -adrenergic blockade is the first line treatment of AF in patients with preserved left ventricular function, and β -adrenergic blockade should also be considered in patients with decreased left ventricular function. (45,46) Landiolol, an ultra- short acting β -antagonist, seems to be fast, effective and safe in converting AF to sinus rhythm in post- operative cardiac surgery patients. (47) At low dose, landiolol facilitates a high rate of conversion to sinus rhythm (69%) in patients with sepsis and supraventricular tachycardia without haemodynamic deterioration. (48)

In a poor prognosis subset of patients with septic shock, i.e. requiring high doses of catecholamines after 24h and with concurrent tachycardia, esmolol demonstrated significant reductions in mortality, time on vasopressors, and renal and myocardial injury compared to the control group. (49) Further studies should confirm the data from this revolutionary idea. In our opinion, the extreme caution in patient selection based on echocardiographically determined preserved systolic and impaired diastolic left/right ventricular function and very low initial dose of ultra-selective β 1-blocker is necessary so as not to induce harm to the critically ill septic patient. (50) In the future, it will probably be important even to determine the pharmacogenetic profile of β -AR in these patients.

Critical illness and management in a critical care unit are characterised by a severe and abnormally prolonged stressor response; this response may become maladaptive. (21) Given this premise, attenuation of an excessive adrenergic component of the stress reaction is a tempting therapeutic option during sepsis and other critically ill states.

Titration of β -blocker dosing to a target heart rate appears feasible without compromising haemodynamics in most patients; stroke volume usually increases while catecholamine requirements decrease. (51) Possible mechanisms include improved ventricular filling and ventricular-arterial coupling; restoration of adrenergic receptor density, which may have been reduced by excessive catecholamine stimulation; (52,53) and a decrease in the systemic inflammatory response. (54)

Patient selection and close monitoring are likely to be crucial in this setting because of the risk of worsening myocardial dysfunction. (21)

The pharmacogenetic properties of β -blockers and an individual approach are, therefore, an important area for further research to further understand which critically ill patients will benefit from both existing and novel therapies for AF and supraventricular tachycardia.

METABOLIC EFFECTS OF B-BLOCKERS

The majority of critically ill patients have a high resting energy expenditure (REE); this is especially true for patients with burns, after severe trauma and in sepsis. (55) Also, patients with heart failure, who are not cachectic, have high REE. (56,57) It has been demonstrated that selective and nonselective β -blockers reduce the REE. (58) Nonselective β -blockers appear to shift total body substrate use from fatty-acid to glucose oxidation. (58-59) As less oxygen is needed for the oxidation of glucose than for the oxidation of fatty acids, (60) this as a favorable effect on myocardial oxygen demand in heart failure. The molecular mechanisms by which nonselective β -blockers promote glucose oxidation are not known, but it has been demonstrated in mice that the receptor NOR-1, which is a target of β -adrenergic signaling, regulates expression of genes that encode proteins that control oxidative metabolism, such as PGC-1 α , lipin-1 α , FOXO1, and the enzyme pyruvate dehydrogenase kinase type 4 (PDK4). (61) This last, PDK4, is an isoform of PDK that is directly involved in the regulation of the entry of glycolysis products into oxidative metabolism. This is also one possible explanation why only the nonselective β -blockers appear to influence the shift of metabolism to glucose oxidation – because they do not only interact with the target β 1-adrenergic receptors. Clinical studies have confirmed the metabolic ef-

fects of non-selective blockers, such as propranolol, on reduced hypermetabolism in burns, which could be prolonged up to 2 years, and carvedilol, which attenuated the development and promoted a partial reversal of cachexia in patients with severe chronic heart failure, supporting a role for prolonged sympathetic activation in the genesis of weight loss. (62,63)

CONCLUSIONS

Catecholamine administration is useful and even life-saving for short-term restoration of tissue perfusion or correction of life threatening hypotension. However, catecholamines are poisonous when given in excess, causing regional ischemia, triggering arrhythmia and promoting systemic inflammation. Individual titration of short-acting, selective β -1 blockers, seems

to be a promising approach to supraventricular tachycardia and to maladaptive response to sepsis, especially in the haemodynamically stable phase of disease. On the other hand, non-selective β -blockers are important regulators of whole body metabolism, capable of reducing resting energy expenditure, attenuating the development and promoting a partial reversal of cachexia.

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