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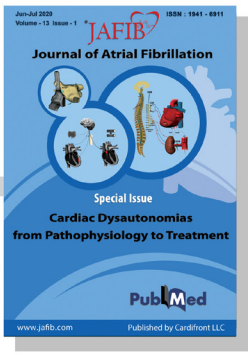

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Impact of Denervation by Heart Transplantation on Post-operative Atrial Fibrillation Susceptibility

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Abstract

Atrial fibrillation is common following cardiac and non-cardiac thoracic surgery and is associated with poorer outcomes, including: increased risk of stroke, hemodynamic instability, prolonged hospital stay, and increased mortality. Current understanding suggests that post-op atrial fibrillation results from the interplay of local and systemic operative inflammation, increased sympathetic activity, perhaps the release of free radical species in the perioperative period, and the patient's underlying cardiac substrate. Cardiac denervation following orthotopic heart transplant (OHT) using modern bicaval techniques presents a unique opportunity to study the relative contribution of the autonomic nervous system to post-op atrial fibrillation susceptibility. Observational studies show a reduced incidence of post-operative atrial fibrillation following orthotopic heart transplant compared to other cardiac and thoracic surgeries. Moreover, comparison of atrial fibrillation rates with double lung transplant recipients suggests that cardiac denervation has a contribution apart from surgical pulmonary vein isolation alone. This report reviews current concepts of the mechanisms of post-op atrial fibrillation with a focus on the role of the autonomic nervous system, the autonomic regulation of the native heart, and evidence regarding the impact of cardiac denervation following OHT.

Introduction

Atrial fibrillation(AF) is common following both cardiac and non-cardiac thoracic surgery, occurring in 20-60% of patients depending on the population studied and the arrhythmia detection used[1-4]. Post-operative (post-op) atrial fibrillation is associated with poorer outcomes, including: increased risk of stroke, hemodynamic instability, prolonged hospital stay, and increased mortality[5-9]. Current understanding suggests that, post-op atrial fibrillation results from the interplay of local and systemic operative inflammation, increased sympathetic activity, and perhaps the release of free radical species in the perioperative period; however, the underlying cardiac substrate also governs a patient's susceptibility.

Cardiac denervation following orthotopic heart transplant (OHT) using current bicaval techniques presents a unique opportunity to study the relative contribution of the autonomic nervous system to post-op atrial fibrillation susceptibility. Comparison with double lung transplant recipients allows the most direct observation of combined surgical pulmonary vein isolation and cardiac denervation, to pulmonary vein isolation (PVI) alone.Although catheter based PVI also disturbs autonomic ganglia, its autonomic and electrophysiological effects are substantially less well understood[10].

This report reviews current concepts of the mechanisms of post-op atrial fibrillation with a focus on the role of the autonomic nervous system, the autonomic regulation of the native heart, and the impact of cardiac denervation following OHT.

Key Words

Denervation, Post-Operative Atrial Fibrillation.

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Mechanisms of post-op atrial fibrillation and role of the autonomic nervous system

Post-op atrial fibrillation is a function of i) chronic factors such as age and comorbid conditions that contribute to atrial myopathy and the cardiac substrate's vulnerability to atrial fibrillation[7, 11, 12] and ii) acute factors related to the physiologic stress of surgery itself.The former has been written about extensively and its review is beyond the scope of this report. Acute factors related to surgery include local and systemic inflammation, increased oxidative stress, and increased sympathetic activation.

The evidence for systemic inflammation as a precipitant of post-op atrial fibrillation is mostly observational, based on several potential contributing factors including: i) the time course of post-op AF correlating with the time course of complement activation and increase in complement-reactive protein[13, 14], interleukin 2[15],

and interleukin 6[16]; ii) increased white blood cell count being an independent predictor of post-op AF in certain studies[17, 18]; and iii) the observation of increased monocyte activation in patients who develop post-op AF[19, 20].

Cardiopulmonary bypass is thought to be an important driver of systemic inflammation, through interaction of blood with the circuit machinery triggering the "alternative pathway" of inflammation, and protamine administration triggering the "classical pathway". Although most studies comparing the rate of post-op AF with "off-pump" and "on-pump" coronary artery bypass surgery failed to show a significant difference in the rate of post-op AF[1,21,22], some randomized controlled trials and a meta-analysis of the same have shown a reduction, admittedly small, in post-AF risk in elderly patients (>70 years old) with off-pump, compared to on-pump, coronary artery bypass surgery[23]. These data suggest that systemic inflammation due to the physiologic stress of surgery makes the larger contribution to provoking post-op AF than does cardiopulmonary bypass.

The data linking local atrial and pericardial inflammation from surgery with post-op AF is conflicting. Two studies examining whether minimally invasive off-pump coronary artery bypass results in less AF than conventional off-pump coronary artery bypass surgery yielded opposing results[24,25], indicating perhaps that any trauma to the pericardium results in sufficient pericardial and atrial inflammation such that the amount of direct myocardial manipulation becomes less important.

As free radicals cannot be readily measured in the myocardial tissue of patients during episodes of post-op AF, supportive evidence for oxidative stress as a contributor comes from measurement of lipid peroxidation products and/or observing the effects of antioxidants on the incidence of post-op AF. In this regard, several issues need consideration. First, patients with post-op AF have been reported to have increased systemic and myocardial oxidative stress[26]. Second, NADPH oxidase activity measured from the right atrial appendage was demonstrated to be the most important independent predictor of post-op AF in patients undergoing coronary artery bypass grafting[27]. Finally, the administration of antioxidant drugs, specifically ascorbic acid[28, 29], N-acetylcysteine[30], sodium nitroprusside[31], and statins[32] (which admittedly also have anti-inflammatory properties) have been shown to reduce the incidence of post-op AF.

Increased sympathetic activity is assumed as a fact to promote post-op AF by increasing myocardial intracellular calcium and consequently atrial ectopy, a trigger of AF, as well as by decreasing action potential duration and reducing the atrial refractory period, which may predispose to localized re-entry and maintenance of atrial fibrillation[33, 34]. Observational evidence supporting the contribution of increased sympathetic activity to post-op AF includes increased norepinephrine levels in patients who develop post-op AF compared to those who do not[35] and increased sinus rate and atrial ectopy prior to onset of post-op AF[36]. Additionally, at least one study reported a decrease in heart rate variability in the hour prior to onset of post-op AF, suggesting that varying autonomic states precede the onset of post-op AF[37]. On the other hand, a discrepancy between the peak of sympathetic activity (within 24 hours) and somewhat later onset of

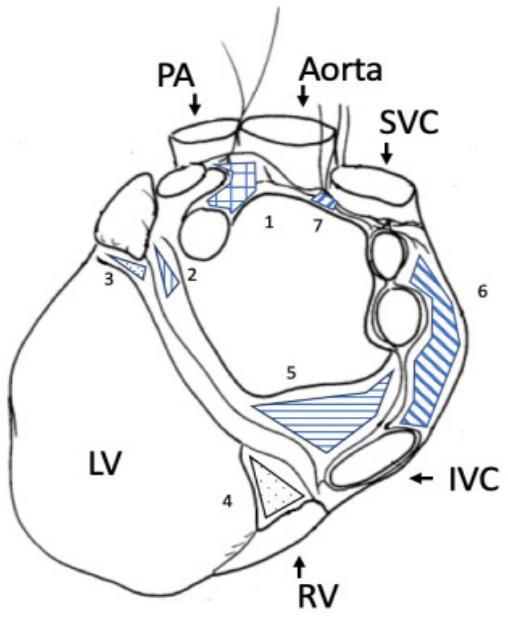

Figure 1: **Posterior schematic view of the heart depicting the general location of the principal atrial and ventricular ganglionic plexi (GPs).**

LA=left atrium, RA=right atrium, LV=left ventricle, RV=right ventricle, IVC=inferior vena cava, SVC=superior vena cava, PA=Pulmonary artery, 1. Superior LA GP, 2. Posterolateral LA GP, 3. Obtuse marginal GP, 4. Posterior descending GP, 5. Posteromedial LA GP, 6. Posterior RA GP, 7. Superior RA GP

AF (typically 48-72 hours) post-operatively[38] suggests that increased sympathetic activation alone is unlikely to explain all post-op AF and that some interplay with the other proposed mechanisms is responsible.

Clinical trials do demonstrate lower rates of post-op AF in patients receiving beta blockers post-operatively but the discontinuation of pre-op beta blockers in the control arm, with its rebound increase in sympathetic innervation of the heart, may have contributed to increased post-op AF in control groups, thereby overstating the effect of beta blockade in reducing post-op AF[39, 40].One nonrandomized clinical trial by Melo et al[41] examined the impact of ventral cardiac denervation on post-op AF in patients undergoing coronary artery bypass grafting.Denervation was carried out after performing the sternotomy and exposing the heart by excising the fat pads surrounding the vena cava, aorta and main pulmonary artery, thereby removing the nerves entering the hilum along the great vessels. Post-op AF was present in significantly fewer patients who underwent this method of denervation than in the control group (7% vs 27%) but only a third of patients in each group were on telemetry and the success of denervation in the intervention group, as measured by resting heart rate or other measures of sympathetic and parasympathetic innervation, was not reported. Recently there has been interest in invasive and transcutaneous low level stimulation of the vagus nerve to reduce post-op atrial fibrillation although only small trials have been conducted thus far[42, 43].

Autonomic control of the native heart

The heart is richly innervated and closely regulated by sympathetic and parasympathetic fibers of the autonomic nervous system.

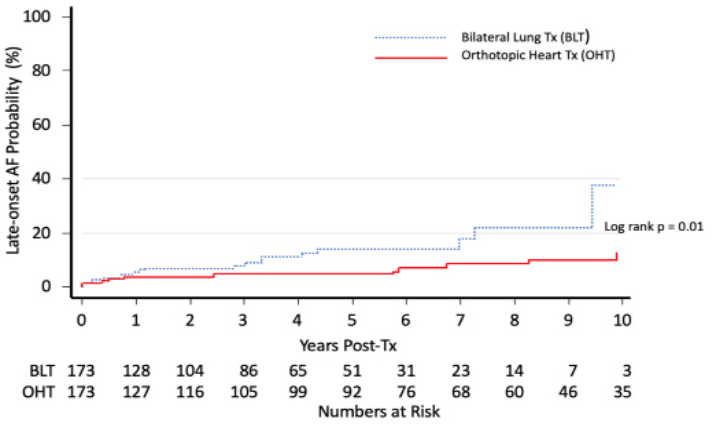

Figure 2: **Probability of late-onset atrial fibrillation among heart vs double lung transplant recipients. Adapted from Magruder et al[75].**

Neural control of the heart takes place at extrinsic (extra-cardiac) and intrinsic (within the heart) ganglia. Extrinsic sympathetic innervation originates from the cervical, stellate, and thoracic ganglia while extrinsic parasympathetic input is transmitted from the medullary brainstem by the vagus nerve[44, 45]. However, sympathetic fibers are also present within vagal nerves[46]. Extrinsic nerves enter the pericardium through the hilum of the heart, its superior posterior region where the parietal pericardium reflects on itself to become the visceral pericardium and where the great vessels pass between the heart and the rest of the thoracic cavity[47]. Within the pericardium the extrinsic nerves distribute into the intrinsic cardiac autonomic system, which comprises ganglionic plexi innervated with both vagal and adrenergic terminals. These ganglionic plexi [Figure 1], located in fat pads around pulmonary vein ostia, the sinus node, and along major coronary artery branches, mediate autonomic inputs that are then transmitted along a network of small nerve fibers[48].The ligament of Marshall nearby the left atrial appendage, too, is richly innervated[49]. Histologic studies of the distribution of acetylcholinesterase- and tyrosine hydroxylase-positive nerves show a greater density of parasympathetic innervation in the atria and a greater density of sympathetic innervation in the ventricles, although various disease states can cause neural remodeling and alter the distribution of adrenoreceptors[50, 51].

Effect of orthotopic heart transplant (OHT) on autonomic inputs to the heart

OHT results in transection of the vagal nerve and the post-ganglionic sympathetic fibers from extrinsic sympathetic ganglia, causing complete denervation of the graft. Axonal degeneration follows, resulting in the disappearance of nerve terminals within the transplanted tissue[52]. Despite loss of the presynaptic neuronal uptake-1 mechanism, which restrains adrenergic activity in the innervated heart through reuptake of norepinephrine into nerve terminals, the graft's response to circulating catecholamines does not approach the response of the native heart to sympathetic input. Reinnervation occurs variably among patients but 40-70% of recipients demonstrate some degree of reinnervation over time. Sympathetic reinnervation seems not to occur until at least 5-6 months after transplant while parasympathetic reinnervation seems to require at least 1-3 years post-transplant. Even then, reinnervation is incomplete and heterogeneous within the graft[53-56].

The loss of autonomic input to the heart has a wide range of immediate effects on cardiac function that variably recover with time as reinnervation restores some autonomic control of the graft. Immediately post-transplant, the resting heart rate increases to reflect the intrinsic heart rate i.e., the age-dependent heart rate in absence of autonomic influences[57], due to absent vagal and reduced sympathetic input. Three years post-OHT, resting heart rates tend to be lower than in recipients less than three years of transplant, suggesting some return of vagal innervation[58]. In comparison to control subjects, OHT recipients also show a slower increase in heart rate with exercise and a lower peak heart rate, a result of reduced sympathetic innervation and reliance on circulating catecholamines alone. Some patients demonstrate nearly no rise in heart rate with physical activity[59, 60].However, several studies show heart rate reserve to increase with time from transplant, suggesting sympathetic reinnervation, and while nearly all recipients in one study had an abnormal heart rate response to exercise two months post-transplant, and nearly half had a normalized response eventually by six months[61, 62]. Heart rate variability, another marker of cardiac autonomic regulation, is markedly reduced in early OHT recipients, reliant only on hormonal and internal (i.e., intra-cardiac) control loops[63].

Like the heart rate at rest and exercise, heart rate variability (HRV) tends to increase with time. In one study, an increase in HRV was observed as early as 15-37 weeks post-transplant in recipients who showed signs of atrial innervation[64]. However, in most studies evidence of reinnervation did not appear until three years or so post-transplant[65, 66].The time course and degree of increase in heart rate variability differed among OHT recipients, another sign that reinnervation occurs heterogeneously and to varying extents between patients.

Data concerning the high-frequency power spectrum, a marker of vagal activity, are less consistent with other studies of parasympathetic reinnervation.Many studies show a lower high-frequency power range in OHT recipients with no improvement up to several years post-transplant, suggesting diminished parasympathetic activity despite other parameters indicating evidence of parasympathetic reinnervation[66, 67].Other studies show an increase in the high-frequency power spectrum with time while others still show no correlation with time following transplant[63, 65, 68].

Other markers of autonomic function including systolic and diastolic blood pressure and catecholamine levels have been studied as well, but have less bearing on the subject of this review. Readers are referred to a paper by Awad et al for a comprehensive review of denervation and reinnervation of the transplanted heart[69].

Evidence regarding the impact of cardiac denervation by heart transplant on post-operative atrial fibrillation

OHT recipients have a much lower rate of post-op atrial fibrillation than patients undergoing other cardiac and non-cardiac thoracic surgery. One small initial study in 1995 reported a rate of 18.2% (16 of 88 patients) but, multiple larger series since have reported AF rates

following transplant of 0.3% (3 of 923 patients), 5.4% (27 of 498), and 7.7% (69 of 892), including those patients who developed AF in close proximity to biopsy-proven rejection, which itself may have been the etiology of AF rather than perioperative factors[70-73]. This low rate of post-op AF occurs despite pericardiectomy significant manipulation of the graft, relatively long ischemic times, and post-operative administration of inotropic agents, all of which would be expected to increase the risk of post-op AF.On the other hand, transplanted hearts tend to be young structurally normal and, perhaps more importantly, immunosuppressive therapy being routinely administered following transplant.

Additional evidence is available in an observational study by Dizon and colleagues[74] examining the rate of post-op atrial fibrillation between 174 consecutive OHT recipients and 122 double lung transplant patients at a single center. Both procedures necessarily result in surgical pulmonary vein isolation but lung transplantation does not transect autonomic inputs to the heart. Only 4.6% of OHT recipients developed post-op AF compared to 18.9% of lung transplant recipients and 19.8% of a comparison group of patients undergoing coronary artery bypass surgery. Both groups received comparable and aggressive immunosuppressive regimens.One difference between the two groups was a higher rate of preoperative beta blocker use in the OHT group (54% vs 13%), although beta blockers are routinely discontinued post-transplant to allow a higher heart rate and contractile function (post-op use was 15% in the OHT group vs 19% in the lung transplant group).No OHT patients received any antiarrhythmic agents post-transplant.Both groups had similar rates of inotrope and vasopressor use.

Magruder and colleagues[75] also studied a cohort of OHT and double lung transplant recipients and reported a lower incidence of late-onset de novo atrial fibrillation in OHT recipients, up to ten years post-transplant [Figure 2].

In another study Noheria and colleagues[76] attempted to examine the incremental value of cardiac denervation after OHT by comparing the rate of post-op AF in transplant recipients to a group of patients undergoing non-transplant cardiac surgery with a left atrial Maze lesion set and another group undergoing coronary artery bypass surgery without any pulmonary vein isolation. Although this report found a significantly lower rate of post-op AF in the transplant group (6.5%) than the Maze (22.7%) and CABG (16.4%) groups, the finding could be partly explained by 96% of the Maze group having had a prior history of atrial fibrillation, compared to just 42% in the OHT group (and it is likely that actually far fewer of the transplanted grafts had experienced atrial fibrillation).

Inflammation likely contributes to post-op atrial fibrillation after heart surgery, but would be expected to be similar after heart transplantation compared to other cardiac procedures. In this regard, our group examined the impact of pre-op statin use on post-op AF following orthotopic heart transplant and found no difference in the rate of post-op AF between recipients who had or had not been on statin therapy pre-operatively[77]. This observation can be interpreted to indicate that, inflammatory suppression has little to offer in the way of atrial fibrillation suppression in the setting of cardiac denervation with immunosuppressive therapy.

Conclusion

New onset atrial fibrillation after cardiac and non-cardiac thoracic surgery is multifactorial. Nevertheless, the reduction in post-op AF after cardiac denervation by OHT in comparison to surgical PVI from double lung transplant or other cardiac surgeries with or without PVI underscores the role of the autonomic system and sympathetic activation in particular. Further studies are warranted to examine the effectiveness of temporary pharmacologic, device based, or invasive autonomic interventions on reducing post-op AF and its associated poorer post-op outcomes.

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