EDITORIAL COMMENT

Postoperative Atrial Fibrillation: A Billion-Dollar Problem*

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Atrial fibrillation (AF) is the most common complication associated with coronary artery bypass graft (CABG) surgery. The impact of postoperative AF on hospital resources is substantial, with annual estimated U.S. expenditures exceeding $1 billion (1) and length of hospital stays increased by a distressing three to four days in the presence of AF (2–4). As a result, postoperative AF represents the most important potentially reversible health care expenditure related to CABG in the U.S., contributing to the cost burden of the “epidemic of AF” (5). Nevertheless, despite significant advances in surgical care, AF incidence stubbornly remains around 20% to 40%, although this is due, in part, to a somewhat-older population of patients undergoing CABG.

Atrial fibrillation clusters tightly in the first two to four days after surgery. Why? In part, this is the result of preexisting electrophysiologic vulnerability in the atria, as evidenced by atrial conduction abnormality (6), but atrial ischemia and reperfusion injury, acute atrial stretch, metabolic derangements, pericarditis, and heightened sympathetic tone (7) may also be contributing factors. Together, the presence of preoperative electrical and structural abnormality with the superimposed postoperative pro- fibrillatory milieu make a volatile mix and foments a high but short-term AF risk.

Pharmacologic therapies have not succeeded in effectively addressing this postoperative problem. For example, a recent meta-analysis (8) concluded that beta-blockers, sotalol, and amiodarone all reduce the incidence of postoperative AF. The beneficial impact on hospital length of stay, however, was small (by less than one-half day), with no evidence of a lowering of stroke events (8). Given these results, it may be advantageous to develop a more complete understanding of why patients with AF are hospitalized longer. Surprisingly, this issue has not been extensively studied, but it is likely to be multifactorial in causation. Although it may be supposed that complications of postoperative AF drive the duration of hospitalization, multivariate analyses have indicated that the simple presence of AF, adjusting for confounding variables, including major complications, is associated with an increased length of stay (9).

If postoperative AF is generally clinically self-limited and uncomplicated, why is it associated with such a substantially longer length of hospital stay? To a large extent, it may be the result of therapeutic interventions, such as drug initiation and titration, the development of drug side effects, the incomplete effectiveness of treatment, and attempts to achieve therapeutic anticoagulation.

If so, it might be worth developing a prospective trial to determine whether length of stay is reduced by a contemporary strategy that foregoes aggressive routine antiarrhythmic drug prophylaxis and concentrates instead on reactive rate-control, cardioversion, and anticoagulants for stroke prevention. These treatments are all readily accomplishable in the outpatient environment. This management approach could be augmented by the routine use of beta-blockers, if not contraindicated, and the use of low-molecular-weight heparin as a bridge to warfarin therapy (11). A simplified strategy also has been proposed by others (3,12). Also promising is the use of atrial pacing to prevent AF after cardiac surgery (13), but the published experience is still rather small. In addition, radiofrequency ablation of pulmonary vein triggers has had remarkable success for nonpostoperative AF, but it is unknown whether a surgical epicardial approach coupled to the routine CABG procedure would be effective and safe nor whether pulmonary vein triggers are important in the postoperative setting.

In this context, the study by Cummings et al. (14) in this issue of the Journal is refreshing and provocative. In patients undergoing CABG, the authors set out to study the anterior fat pad, located in the aortopulmonary window, which is routinely removed during the process of placing the aortic cross-clamp, the aortic cannula for cardiopulmonary bypass, and aortic grafts. Because the fat pad contains nervous tissue, the study sought to determine whether it contained parasympathetic ganglia, as previously described in dogs (15,16), and whether its dissection would decrease subsequent AF. Because enhanced vagotonia is pro- fibrillatory in the atria by shortening refractoriness, the underlying assumption was that by removing tissue responsible for vagal atrial influences, an improved AF outcome would result. The autonomic nervous system has long been thought to play a role in AF after cardiac surgery but mediated by an enhanced adrenergic state. The importance of the parasympathetic nervous system has not received much attention in this setting, although it is known to play a role in subsets of patients with paroxysmal nonpostoperative AF (17).

The sinus node, the atrioventricular node, and atrial
tissue all have extensive cholinergic innervation and are highly sensitive to vagal influences. Vagal postganglionic neurons are located in distinct anatomic fat pads, distributed around the heart and adjacent structures. The fat pad located between the right pulmonary veins and right atrium contains fibers that predominantly influence the sinus node, and the fat pad located between the inferior vena cava and the left atrium contains fibers that largely modulate AV nodal function. Elegant experimental work has recently elucidated the functional importance of a third “anterior” fat pad: it either serves as a “head station,” distributing fibers to the sinus and AV nodes and to both atria (15), or as a “modulator” of atrial electrical and contractile function (16). Selective destruction of this fat pad during animal experiments produced complete or partial vagal denervation of the right atrium, left atrium, or both, although with variable consistency (15). If complete bilateral denervation can be accomplished in experimental models, sustained AF can be prevented (15,18).

In the study by Cummings et al. (14), the anterior fat pad was localized in 55 patients undergoing CABG. Stimulation of the fat pad resulted in sinus rate slowing, with no change in PR-interval, indicating a direct or indirect innervation of the sinus node but not the AV node. When the fat pad was dissected, the vagal effect on sinus rate was lost. Unfortunately, a critical examination of the effect on atrial refractoriness during stimulation of the anterior fat pad was not performed. This leaves open the question of whether this fat pad influences atrial electrophysiology in humans, that is, refractoriness, and in which atrium. Indeed, pathologic confirmation of the neural components of this fat pad also was not undertaken.

Patients were then randomized into two groups, one in whom the anterior fat pad was dissected (as is typical in CABG) and one in whom the fat pad was deliberately preserved. The authors anticipated an antiarrhythmic effect on AF when the fat pad was removed; however, the opposite was observed: 11 of 29 patients (37%) with a dissected anterior fat pad developed AF compared with only 2 of the 26 patients (7%) with a preserved anterior fat pad (p < 0.01). Importantly, only the dissected fat pad group had clinically significant AF.

The study was small and will clearly need confirmation before the findings can be considered conclusive. The study’s findings may simply be the play of chance. Interestingly, a previous study has provided a measure of replication in that anterior fat pad preservation also decreased AF incidence (19). Support for the authors’ findings can also be found in the literature (20,21) that reports a lower incidence of AF after off-pump CABG, during which the anterior fat pad is often preserved. It is, however, important to account for the generally lower-risk profile of patients who undergo off-pump CABG, which would contribute to a lower AF risk (22).

If the results of the present study are confirmed in future investigation, it could have important implications for solving the aforementioned costly and hospital lengthening effects associated with postoperative AF. Notably, this surgical approach is reputed to be in no way disadvantageous to the performance of CABG itself. Accordingly, pending further confirmation, these results illustrate how a relatively innocuous surgical maneuver can have unforeseen important consequences.

The current study also raises a series of intriguing questions. First, why did removal of the anterior fat pad prove proarrhythmic? As the authors suggest, it may be that the balance of sympathetic and parasympathetic regulation was upset with loss of the anterior fat pad. Alternatively, as heterogeneity of refractoriness is so important in promoting reentry as the mechanism of AF, it is quite possible that heterogenous loss of atrial innervation (partial denervation) (23), which may result if the anterior fat pad was removed, aggravates a critical determinant of AF.

The data of Cummings et al. (14) suggest that partial denervation is disadvantageous, at least after cardiac surgery. Animal experiments endorse complete vagal denervation as an effective antiarrhythmic strategy (18). Should all three fat pads be dissected, rather than only one, when CABG or other cardiac surgery is performed? Is complete denervation more effective than preserved innervation? Do outcomes differ for postoperative AF versus nonpostoperative AF? Is high vagal tone a prerequisite for antiganglionic strategies, or are all patients at risk of AF sensitive to therapeutic, inadvertent, or pathologic modulation of cholinergic neural control? Are there important detrimental effects on sinus node or AV node function, or other autonomic cardiac responses, when fat pads are removed? More investigative work in the laboratory and in the operating room is required to address each of these issues.

In summary, the mechanisms of AF continue to be unraveled, often in unexpected ways. The importance of vagal influences and the cardiac fat pads on postoperative AF deserves extensive additional clinical research to determine the most optimal surgical technique and best overall multidisciplinary antiarrhythmic strategies. Although this new road may represent the path to finally solving the “billion-dollar” problem of resistant AF after coronary bypass surgery, it must now face the test of repeated trials.

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