Perioperative Anesthetic Management In Heart Transplanted Recipients Undergoing Noncardiac Surgery

Essay

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ACE	Angiotensin-converting enzyme
ANP	Atrial natriuretic peptide
ARB	Angiotensin receptor blockers
ARDS	Adult respiratory distress syndrome
ATG	Antithymocyte globulin
ATGAM	Antithymocyte gamma-globulin
AV	Atrioventricular
BNP	B-type natriuretic peptide
BP	Blood pressure
CAD	Coronary artery disease
CARGO	Cardiac allograft gene expression observation
CAV	Cardiac allograft vasculopathy
CHF	Congestive heart failure
CMV	Cytomegalovirus
CNS	Central nervous system
CSA	Cyclosporine
CVP	Central venous pressure
DM	Diabetes mellitus
EBV	Ebstein-Barr virus
ECG	Electrocardiogram

EDV	End-diastolic volume
EF	Ejection fraction
EMB	Endomyocardial biopsies
Epi	Epinephrine
FDA	Food and drug administration
GIT	Gastrointestinal
GMP	Guanosine monophosphate
HDL	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HR	Reart rate
HSV	Herpes simplex viruses
IL-2R	Interleukin-2 receptor
IMP	Inosine monophosphate
ISHLT	International society for heart and lung transplantation
IUGR	Intrauterine growth retardation
IV	Intravenous
IVUS	Intravascular ultrasound
LDL	Low-density lipoprotein cholesterol
MAC	Minimum alveolar concentration
MMF	Mycophenolate mofetil

MPS	Mycophenolate sodium
MRI	Magnetic resonance imaging
NDMR	Nondepolarizing muscle relaxant
NE	Norepinephrine
NSVT	Nonsustained ventricular tachycardia
OHT	Orthotopic Heart Transplant
PAP	Pulmonary artery pressure
PCP	Pneumocystis carinii pneumonia
PTLD	Post-transplant lymphoproliferative disease
PVCs	Premature ventricular beats
RBBB	Right bundle branch block
SA	Sinoatrial
SV	Stroke volume
TAC	Tacrolimus
TEE	Transesophageal echocardiography
TNF	Tumor necrosis factor
TOR	Target of rapamycin inhibitors.
VLDL	Very low-density lipoprotein
VVO Pace maker	It paces the ventricle, senses the ventricle with fixed rate

INTRODUCTION

Heart transplantation as a treatment for end-stage heart disease proved to be an accepted therapeutic modality only after the introduction of cyclosporine immunosuppression in the early 1980s ***(Pochettino A. et al., 2000)***.

Survival statistics reported by the International Society of Heart and Lung Transplantation (ISHLT) showed improved long-term survival that implies a further rise in the population of living cardiac allograft recipients and so, increased chance that anesthesiologists encounter those patients in their daily practice ***(Manuel L. and Stanley H., 1997).***

The cardiac transplant recipient may return to the operating room for a minor surgical procedure, such as incision and drainage of a skin abscess, or for major surgeries, such as laparotomy for perforation of the bowels, stomach, and esophagus, and laparotomy for pancreatic disease, cholecystitis, appendicitis, and incarcerated inguinal hernias ***(Kostopanagiotou G. et al., 1999).***

The cause of these complications is multifactorial. The debilitated preoperative condition of the recipient consequent to circulatory failure and nutritional deficits, accentuated by the stress of surgery, may make those patients more susceptible to complications after transplantation. In addition, immunosuppressive therapy may directly or indirectly contribute to both early and late complications (***Manuel L. and Stanley H., 1997).***

PATHOPHYSIOLOGY OF THE TRANSPLANTED HEART

Heart transplantation is a widely accepted therapy for most patients under 65 years of age with advanced heart failure who remain symptomatic with the expectation of high or intermediate term mortality, despite optimal heart failure medications. Heart transplantation should be reserved for those patients most likely to benefit in terms of both life expectancy and quality of life. With over 30 years of experience, heart transplantation has been the most scrutinized and intensively studied therapy for advanced heart failure ***(Kirklin JK. et al., 2004).***

Today, the better understanding of immune mechanisms in allograft rejection and the subsequent development of new immunosuppressive treatment regimens, improved postoperative follow-up care management. Moreover new donor organ preservation and transport systems, dramatically improves survival rates for heart transplant recipients. Recent data from the ISHLT registry have shown that the overall graft half-time (time at which 50% of those transplanted remain alive) has been increasing steadily, nowadays reaching over 10 years ***(Taylor DO. et al., 2008).***

Physiology Of Cardiac Nerves

A thorough knowledge of the principles of cardiovascular physiology is the foundation for the practice of cardiovascular anesthesia. It serves as the basis of understanding the patient's pharmacologic and surgical management.

Sympathetic System

Nerves of the heart originate from sympathetic neurons of thoracolumbar region. Sympathetic fibers come from the stellate ganglion and the caudal halves of the cervical sympathetic trunks below the level of the cricoid cartilage. Transmission through the sympathetic ganglia occurs by release of acetylcholine, which interacts with the postsynaptic nicotinic cholinergic receptors on the postganglionic neurons. This stimulates norepinephrine release at the neuroeffector junction to activate B_1 adrenergic receptors ***(Janes RD. et al., 1986).***

Parasympathetic System

Parasympathetic preganglionic neurons arise in the medulla oblongata in the dorsal vagal nucleus and the nucleus ambiguous. These fibers enter the thoarx as branches from the recurrent laryngeal and thoracic vagus nerve. Ganglia within the heart usually close to the structures innervated by the short postganglionic neurons. Postganglionic transmission occurs from stimulation of nicotinic cholinergic receptors at the postganglionic junction by acetylcholine. Release of acetylcholine at the neuroeffector junction activates muscarinic receptors in the heart ***(Carol L., 1996).***

Neural Regulation

Although the dominance of either the sympathetic or the parasympathetic system varies with age, situation, and physical condition, the inhibitory parasympathetic system is usually predominant. Parasympathetic stimulation, particularly of the right vagus nerve, decrease heart rate by

slowing the sinoatrial (SA) node. Vagal stimulation tends to suppress ventricular automaticity, which may facilitate termination of ventricular dysrhythmias. Intense vagal stimulation depresses both atrial and ventricular contractility by stimulation of cardiac muscarinic receptors ***(Marneffe M. et al., 1986).***

Stimulation of the stellate ganglion or other sympathetic cardiac fibers increases heart rate (HR), contractility, and ejection fraction (EF). The right stellate ganglion has a greater effect on HR, whereas the left has more effect on contractility. Abnormalities of sympathetic cardiac nerve tone occur in long QT interval syndromes ***(Carol L., 1996).***

Physiology Of The Denervated Heart

Cardiac denervation is an inevitable consequence, as the cardiac plexus is divided in the donor, resulting in a denervated donor heart ***(Ramakrishna H. et al., 2009).***

The atrial remnant of the recipient remains innervated, but no impulses will cross the suture line. As a result, the donor atrium is responsible for heart rate generation. The transplanted heart has a higher intrinsic rate and reduced rate variability. Resting heart rates range from 90 to 110. The loss of vagal input causes an increase in automaticity of the sinoatrial (SA) and atrioventricular (AV) nodes ***(Keegan MT. and Plevak DJ., 2004).***

Normal responses to changes in position, e.g. orthostatic changes, are lost as are the variation in response to stimuli such as the Valsalva manoeuvre,

carotid sinus massage as well as normal responses to laryngoscopy and intubation ***(Kostopanagiotou G. et al., 1999).***

Intrinsic function such as cardiac impulse formation and conduction are intact. The Frank-Starling mechanism is also intact. In the innervated heart, the normal acute response to sudden reduction in intravascular volume is simultaneous increase in both heart rate and contractility ***(Ramakrishna H. et al., 2009).***

In the denervated heart there is an increase in cardiac output in the exercise state, however the mechanisms involved in the increase are different in the early stages than in the late stages of exercise. As opposed to normal hearts which initially increase output predominantly using rate, at the beginning of exercise, transplant patients increase output using Frank-Starling mechanisms by increasing the stroke volume (SV) and end-diastolic volume (EDV) ***(Keegn MT. and plevak DJ., 2004).***

This is mediated through the autonomic nervous system which still controls the splancnic bed. At maximal exercise the EDV is equal to that of resting state; however there is an increase in the heart rate, ejection fraction and stroke volume all due to the increase of circulating catacholamines (***Manuel L. and Stanley H., 1997).***

The transplanted heart is, therefore, critically preload dependent; higher filling pressures are needed, and this has to be kept in mind before the induction of general and regional anethesia (***Manuel L. and Stanley H., 1997).***

A further study showed that, reinnervation is an ongoing process with different effects on various regions of the heart and not completed until 15

years after transplantation. Reinnervation affects the sensation of chest pain, regional regulation of myocardial blood flow and substrate metabolism also ventricular function and exercise performance will improve ***(Bengel FM. et al., 2000).***

Denervation And Pharmacodynamic

The actions of the sympathetic and parasympathetic nerve signals on the cardiovascular system are regulated by several means, including presynaptic receptors (adrenergic or cholinergic), which promote or inhibit neurotransmitter release. After denervation, these regulatory processes are no longer functional and "normal" response to cardioactive and vasoactive agents may be altered because of presynaptic consequences of nerve loss or postsynaptic changes related to the respective receptor-effector system ***(Bristow MR., 1990).***

Drugs whose cardiovascular actions are dependent on the autonomic nervous system (atropine, edrophonium, hydralazine, pancuronium) have no effects in the denervated heart (Table 1***)*** (***Manuel L. and Stanley H., 1997).***

Isoproterenol and dobutamine have similar effects in both denervated and normal hearts. Therefore, they are both effective inotropes in the denervated heart. They increase myocardial contractility more than dopamine ***(Manuel L. and Stanley H., 1997).***

Drugs	Heart Rate		Blood Pressure	
	Innervated	Denervated	Innervated	Denervated
Atropine	↑	NR	↑±	NR
Edrophonium	↓	NR	NR	NR
Neostigmine	↓	NR	NR	NR
Pancuronium	↑	↓	NR	NR
Hydralazine	↑	NR	↓↓	↓↓
Amyl nitrite	↑	NR	↓	↓↓
Digoxin	↓	NR	NR	NR
↑=increase; ↓= decrease; NR= no response; ↑±=either small increase or no change.				

Table (1) Indirect Acting Cardioactive Drugs ***(Manuel L. and Stanley H., 1997).***

Similarly *sympathomimetic* drugs that act indirectly by releasing neuronal norepinephrine(NE) have a blunted effect on transplanted hearts (Table 2) ***(Csete M. and Sopher MJ. , 1994).***

Drugs	Mechanism of Action	Cardiovascular Response	
		Innervated	Denervated
Ephedrine	Direct action: stimulation of beta-1, beta-2 and alpha. Indirect action: through release of neuronal norepinephrine(NE).	↑HR and BP	Blunted response
Metaraminol	Alpha-1(predominant) and beta-1; causes release of NE; with chronic use , act as a false neurotransmitter	↓ HR (reflex) and ↑ BP	BP response may be blunted; HR may ↑ (loss of baroreflex)
Dopamine	Alpha-1, alpha-2, beta-1, beta-2 and dopaminergic ; can also cause release of NE	↑ HR and ↑ BP (dose dependent)	Acts predominantly as a dopaminergic and vasoconstrictor
Mephentermine	Alpha-1, beta-1? beta-2; causes release of NE	↑ HR and ↑ BP(greater chronotropic effect)	Blunted response
HR=heart rate; BP=blood pressure; ↑=increase; ↓=decrease; ? =question.			

Table (2) Mixed direct and indirect acting sympathomimetic drugs ***(Csete M. and Sopher MJ., 1994).***

Nonadrenergic inotropes, including the phosphodiesterase inhibitors (i.e., milrinone, amrinone, aminophylline, and glucagon), continue to be effective in the denervated heart. Because deafferentation and de-efferentation