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PAPERS, POSTERS, PRESENTATIONS:
COMMUNICATING THE BIOMEDICAL SCIENCES
The target journal: choosing the right place to submit your paper
M. John
I punti fondamentali del nostro lavoro sono stati:
- definire i criteri utili ad indicare la necessità di una consulenza rianimatoria nel quadro clinico evolutivo di Insufficienza Respiratoria;
- definire i criteri minimi indispensabili per poter identificare un’Unità di Terapia Intensiva in un Referral Centre per il trattamento dei casi più gravi.

Un dato infatti emerge prepotentemente dallo studio dei livelli organizzativi di coloro che hanno già affrontato le conseguenze dell’infezione da AH1N1: i casi più difficili ed i quadri più gravi di insufficienza respiratoria acuta devono essere centralizzati in Unità di Terapia Intensiva predisposte per la cura con le tecniche più avanzate.

Di seguito riporto i primi dati parziali del nostro lavoro.
Indicazioni di massima per consulenza rianimatoria.
Una consulenza rianimatoria è indicata, di massima, in pazienti con sintomatologia respiratoria, storia clinica ed obiettività compatibile con influenza AH1N1 (da accertare tempestivamente qualora non si sia proceduto) ove si verifichi almeno una delle seguenti condizioni:

a) Sat cap<90% con maschera O2 10 l/min
oppure
b) Acidosi respiratoria  (pH <7.25)
oppure
c) Evidenza clinica di imminente distress respiratorio o frequenza respiratoria >35 atti/min
oppure
d) incapacità di proteggere le vie aeree (Glasgow Coma score <8)
oppure
e) Ipotensione: Pressione sistolica arteriosa <90 mmHg + alterati livelli di coscienza + contrazione della diuresi + mancata risposta al carico volemico.

Nota Bene: non si tratta di criteri che indichino il ricovero in Rianimazione nè l’intubazione. L’indicazione per il ricovero è decisa dall’anestesista rianimatore dopo valutazione collegiale del quadro clinico specifico.

I pazienti destinati a ricevere trattamento convenzionale sono stati lasciati negli ospedali in cui erano ricoverati e curati senza un protocollo definito, ma con la raccomandazione di utilizzare strategie di ventilazione protettiva.
I pazienti destinati a ricevere trattamento con ECMO sono stati
trasferiti in un unico centro nazionale di riferimento. Il 63% dei pazienti destinati a ricevere ECMO sono sopravvissuti a 6 mesi senza disabilità severa contro il 47% del gruppo di controllo. Dei 90 pazienti destinati a ricevere ECMO, 68 (75%) sono stati effettivamente trattati con questa metodica mentre 17 (migliorati dopo la randomizzazione) sono stati trattati con metodiche convenzionali, 14 di questi pazienti sono sopravvissuti. Questi soggetti non sono stati esclusi dalla casistica ma lasciati nel gruppo ECMO considerando come preponderante l’’intent-to-treat”. Il trattamento con ECMO si traduce in un aumento dei costi di circa 45.000 Euro/paziente che sembrano essere compensati, anche da un punto di vista economico, dalla maggior sopravvivenza e qualità della vita.

Editor in Chief
Professor Alberto Zangrillo

BIBLIOGRAFIA

The role of recombinant activated factor VII in cardiac surgery

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ABSTRACT
Recombinant factor VIIa may reduce surgical blood loss and transfusion of blood products in cardiac surgery. However, the true risks of its use in this setting remains to be elucidated, especially when it is administered with other potent pro-haemostatic agents. We reviewed the recent literature on this topic and suggest that the off label use of recombinant factor VIIa is likely to continue. It is our institutional practice to use it in the operating room at a dose of 90mcg/Kg to ensure there is no obvious correctable surgical source of blood loss, and to be certain that bleeding has stopped before the chest is closed.

Keywords: recombinant factor VII, cardiac surgery, bleeding, transfusion.

INTRODUCTION
Bleeding is a common complication following cardiac surgery, leading to transfusion and/or surgical re-exploration. Both interventions are associated with significant cost, in terms of both risk to the patient and financial outlay to the healthcare system (1).

Perioperative allogeneic red cell and haemostatic component transfusion has been shown to be associated with increased length of intensive care unit and hospital stay (2), increased infection rates (3), increased rates of every postoperative morbidity event (4), and decreased short- and long-term survival rates (5, 6).

Re-exploration is associated with significant increases in mortality, the need for intra-aortic balloon counter-pulsation, haemofiltration, prolonged ventilation and intensive care unit stay (7). Novel haemostatic agents may have role in reducing surgical blood loss and the associated transfusion of blood products.

RECOMBINANT FACTOR VIIA
Recombinant factor VIIa (rFVIIa) is licensed for the prevention and treatment of bleeding in patients with haemophilia with auto-antibodies to coagulation factors VIII or IX, FVII deficiency, and acquired haemophilia. The binding of VIIa to perivascular tissue factor (TF) initiates coagulation, although the process can only progress beyond the generation of small amounts of thrombin when the injury allows platelets and larger proteins to leave the vascular space and adhere to TF-bearing cells in the perivascular area. However, TF may also be expressed on activated neutrophils, monocytes and microparticles.

The exact role of this circulating TF remains...
controversial, as under normal conditions it is thought to be inactive or encrypted (8). Thus, although the effects of VIIa are believed to be localized predominantly to the site of vessel injury, concerns remain about the potential for thrombotic complications arising from its use. The complex nature of haemostasis and the role rFVIIa plays have been previously described (9).

USE

The medical literature increasingly describes “off-label” rFVIIa use to treat severe bleeding after major surgery in patients without haemophilia. Whilst some studies have used it to prevent bleeding and transfusion (prophylaxis), the majority have used it as rescue therapy when conventional surgical exploration and blood product and anti-fibrinolytic agent administration has failed to arrest bleeding. It has therefore rarely been studied in isolation from other pro-haemostatic agents. The majority of trials have reported on rFVIIa use in adults; some have examined the paediatric population. The range of surgical procedures in which it has been used has been comprehensive, with a significant rate of redo cardiac surgery in the adult setting (10).

DOSE

The optimal dosing regime for rFVIIa in the post-cardiac surgical setting remains unclear. The reported dose range for single bolus administration has been broad (11.1 – 180 mcg/kg), although many have used single doses of 90 mcg/kg or less. Some studies have limited treatment to a single bolus dose, whilst others have used repeated doses at varying intervals. Recommendations made by various expert panels have suggested doses in the order of 40-100 mcg/kg in the setting of uncontrolled post-cardiac surgical haemorrhage, with second doses considered if no response is seen after 30 to 60 minutes (10).

Efficacy

The consensus is that rFVIIa reduces bleeding after cardiac surgery, as evidenced by a reduction in chest tube drainage and red cell and component therapy transfusion rates. Some authors have found that these effects are more sustained with increasing rFVIIa doses. There is also evidence that rates of surgical re-exploration for bleeding are reduced (11, 12). However the majority of trials have been underpowered, whilst case reports and series are subject to positive reporting and publication bias.

Adverse Events

Since cardiopulmonary bypass may up-regulate the expression of systemic tissue factor, the main focus of concern has been inappropriate thrombosis associated with rFVIIa use in the cardiac surgical setting. Interestingly, the incidence of adverse thrombotic events is almost zero in the paediatric population. This may have something to do with their naive vascular endothelium. Observational uncontrolled data from the US Food and Drug Administration adverse event reporting system reveals an alarming 1 in 50 thromboembolic complication rate (associated with a 0.5% mortality) when “off label" rFVIIa is used in a diverse range of patients (13). In cardiac surgery, mortality and complication rates of patients who have failed to respond to standard transfusion therapy and then received rFVIIa are within range of 19% to 40%. The lack of control pa-
patients in most of these case series makes it difficult to determine whether the reported adverse events are related to the administration of rFVIIa or the critical unstable condition of patients when they received rFVIIa (14-17). When rFVIIa has been used on a compassionate basis to reduce uncontrolled bleeding in 51 patients after cardiac surgery, propensity matching techniques to adjust for baseline risks indicated that the rates of serious adverse events were equivalent (18). In a group of patients with a very high risk of stroke, a matched analysis of patients receiving rFVIIa after major ascending and aortic arch reconstructive surgery suggested stroke rates were equal (19). A recent multicentre randomized clinical trial of rFVIIa in patients actively bleeding after cardiac surgery showed a non-significant trend to an increase in the rates of thromboembolic complications. This trial demonstrated a 50% reduction in reoperation rates for bleeding and as expected a marked dose-dependent decrease in transfusion rates in those patients randomized to rFVIIa (11).

DISCUSSION

There appears to be general agreement that rFVIIa has the potential to reduce bleeding, blood product administration and re-operation rates post-cardiac surgery. However, these are not outcomes in themselves, and the true risks of its use in this setting remain to be elucidated, especially when it is administered with other potent pro-haemostatic agents. The under-powering of trials performed to date mean that differentiation between adverse events arising specifically from rFVIIa use, and arising generally from the critical condition of those receiving is currently impossible. There has also been a lack of longer-term follow-up in studies in this context. Thus, it remains to be seen whether rFVIIa use may reduce the mid- to late-term complications of red cell transfusion, such as pulmonary dysfunction and sepsis. There is currently no consensus on the appropriate “off-label” dose of rFVIIa. Since the thrombin-generation response to VIIa depends on the availability of other coagulation factors and platelets, it would seem that the ‘optimal’ rFVIIa dose will vary according to the degree of transfusion of other blood products. This will need to be accounted for when planning future studies. Given the uncontested efficacy of rFVIIa in preventing and reducing bleeding and transfusion, its “off label” use is likely to continue.

Clinicians must be aware of both the potential risk and benefits when using this potent thrombin-generating agent. It is our institutional practice to use it in the operating room at a dose of 90 mcg/Kg to ensure there is no obvious correctable surgical source of blood loss, and to be certain that bleeding has stopped before the chest is closed.

Dr Herbertson and Dr Gill worked on advisory boards for Novo Nordisk; Dr Gill received speaker fees from Novo Nordisk.

REFERENCES

Acute renal failure and cardiac surgery

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ABSTRACT

Acute renal failure (ARF) is a major complication after cardiac surgery and its prevalence still remains high. Even minor changes in serum creatinine are related to an increase morbidity and mortality. Recently two consensus conferences have suggested new diagnostic criteria to define acute kidney injury and risk scores to better identify patients who will probably develop ARF after cardiac surgery. In fact a prompt recognition of high risk patients could allow a more aggressive therapy at a reversible stage of an incoming ARF. To date prophylactic strategies of renal function preservation during surgery include the avoidance of nephrotoxic insult and the prevention or correction of renal hypoperfusion. Although there are still no pharmacological agents able to prevent the perioperative ARF, several trials are investigating new pharmacological approaches. When prophylactic strategies fail and severe ARF occurs, renal replacement therapy becomes mandatory. The timing and the kind of renal replacement therapy remain an open issue. Further randomized case-control studies with adequate statistical power are needed to have more conclusive data. Aim of this paper is to start from the acute renal injury physiopathology to analyze the most common prophylactic and pharmacological strategies.

Keywords: acute renal failure, acute kidney injury, renal replacement therapy, cardiac surgery.

Acute renal failure (ARF) still remains a major complication after cardiac surgery. Even minor changes in serum creatinine are related to an increase morbidity and mortality. As recently shown by Chertow et al. (1), ARF “per se” is an independent determinant of mortality as much as cardiac arrest. The true incidence of acute renal failure in patients undergoing cardiac surgery is still unknown because different authors have used different nomenclature to define ARF. To sort out this lack of uniformity in 2004 the Acute Dialysis Quality Initiative Group (ADQI) published the Rifle criteria (2). RIFLE is the acronym of 3 severity grades (Risk, Injury and Failure) identified on the basis of the creatinine serum variation or urine output (the worst between them is considered), and 2 outcomes (Loss and End-Stage Kidney Disease) related to the length of loss of kidney function (Table 1). The 3 classes of severity have a higher sensitivity than specificity, on the other hand the 2 categories related to the length of the kidney function loss have a low rate of false negative.

In September 2004 the ADQI group, the representatives of three nephrology societies, and the European Society of Intensive Care Medicine in Vicenza, Italy have introduced the concept of acute kidney injury (AKI) including the entire spectrum of ARF. In the same meeting they created the Acute Kidney Injury Network (AKIN).
as independent multidisciplinary collaborative network formed by experts selected by the participating societies (3) (Table 2).

As in the RIFLE score, in the AKI system the main criteria to classify the renal failure stage are the creatinine serum variation and/or the urine output. Major advantages of the new staging system classification for acute kidney injury are:

1) a more flexible interim classification of the renal failure (a patient on RRT is classified as stage 3 regardless of the severity class at the time of the start of the RRT) and

2) a more accurate detection of the AKI.

Using the RIFLE criteria the incidence of AKI after cardiac surgery is considerably higher than previously reported incidence of ARF (15-20%) in 2 large studies (4, 5).

Table 1 - The RIFLE scale, modified by Bellomo et al. (2).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum creatinine criteria</th>
<th>Urine output criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>Serum creatinine increased 1.5 times or GFR decrease &gt; 25%</td>
<td>&lt; 0.5 ml/kg/h for 6 h</td>
</tr>
<tr>
<td>Injury</td>
<td>Serum creatinine increased 2.0 times or GFR decrease &gt; 50%</td>
<td>&lt; 0.5 ml/kg/h for 12 h</td>
</tr>
<tr>
<td>Failure</td>
<td>Serum creatinine increased 3.0 times or GFR decrease &gt; 75% or creatinine &gt; 4 mg/dl (Acute rise &gt; 0.5 mg/dl)</td>
<td>&lt; 0.3 ml/kg/h for 24 h or anuria for 12 h</td>
</tr>
<tr>
<td>Loss</td>
<td>Persistent acute renal failure; complete loss of kidney function for longer than 4 weeks</td>
<td></td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>End stage renal disease for longer than 3 months</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 - Classification/staging system for acute kidney injury (AKI). Modified from Metha et al. (3).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum creatinine criteria</th>
<th>Urine Output Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Increase in serum creatinine of more than or equal to 0.3 mg/dl or increase to more than or equal to 150% to 200% (1.5-to 2-fold) from baseline</td>
<td>Less than 0.5 ml/kg per hour for more than 6 hours</td>
</tr>
<tr>
<td>2</td>
<td>Increase in serum creatinine to more than 200% to 300% (&gt; 2-to3-fold) from baseline</td>
<td>less than 0.5 ml/kg per hour for more than 12 hours</td>
</tr>
<tr>
<td>3</td>
<td>Increase in serum creatinine to more than 300% (&gt; 3-fold) from baseline (or serum creatinine of more than or equal to 4.0 mg/dl with an acute increase of at least 0.5 mg/dl)</td>
<td>Less than 0.3 ml/kg per hours for 24 hours or anuria for 12 hours</td>
</tr>
</tbody>
</table>
which ranges from mild changes in markers of renal function, (i.e. creatinine and urea), until the complete renal failure.

In particular elderly patients are vulnerable to prerenal azotemia because of their predisposition to hypovolemia and high prevalence of renal-artery atherosclerotic disease. In this kind of patients, who are often affected by large-vessel or small-vessel renal vascular disease, the therapy itself plays an important role, in fact, a combination of angiotensin-converting-enzyme inhibitors and diuretics can worsen the renal failure increasing the hypovolemia.

The low cardiac output syndrome can lead to kidney ischemia after cardiac surgery either decreasing the renal flow or changing the renal physiology.

During the CBP the non pulse blood flow, the macroembolic and microembolic insults to the kidney (organic and inorganic debris), the release of catecholamines and inflammatory mediators such as the free hemoglobin from traumatized red blood cells increase the renal vascular resistances and decrease the glomerular filtration rate of the 25-75% compare to the perioperative period.

Often the ischemic renal injury is reversible after the correction of the underlying causes, but if the ischemia is severe the cortical necrosis is irreversible.

However the kidney can restore its structure and function also after severe ischemia by the spreading and dedifferentiation of viable cells.

From the clinical point of view the early post cardiac surgery AKI is strongly associated with two major factors: reduced functional reserve and renal ischemia. Chertow has defined the renal ischemia occult, because asymptomatic, silent, unlike myocardial and cerebral ischemia. For these reasons the development of scores able to predict the ischemic AKI becomes mandatory (6).

**PREDICTIVE SCORES**

The Continuous Improvement in Cardiac Surgery Program (CICSP) score is a good predictor of AKI in a cardiac surgery population (6). The CICSP risk-stratification algorithms has been developed and validated in 43 Department of Veterans Affairs medical centers between the 1987 and the 1994. It includes the following risk factors: low ejection fraction ≤35 % (2 points); valvular surgery (3 points); chronic obstructive pulmonary disease (2 points); NYHA functional class IV (2 points); peripheral vascular disease (2 points); preoperative use of an intra-aortic balloon pump (5 points); prior heart surgery (3 points); pulmonary rale (2 points); systolic blood pressure >160 mmHg and CABG surgery (3 points); systolic blood pressure ≤120 mmHg and valvular surgery (2 points); and creatinine clearance 80 to 100 mL/min (2 points), 60 to 80 mL/min (3 points), 40 to 60 mL/min (5 points), ≤40 mL/min (9 points).

**Table 3 - The Thakar score (Minimum score 0; maximum score 17). Modified from Thakar et al. (7).**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>1</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt; 35%</td>
<td>1</td>
</tr>
<tr>
<td>Preoperative use of IABP</td>
<td>2</td>
</tr>
<tr>
<td>CoPD</td>
<td>1</td>
</tr>
<tr>
<td>Insulin-requiring diabetes</td>
<td>1</td>
</tr>
<tr>
<td>Previous cardiac surgery</td>
<td>1</td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>2</td>
</tr>
<tr>
<td>Valve surgery only (reference to CABG)</td>
<td>1</td>
</tr>
<tr>
<td>CABG + valve (reference to CABG)</td>
<td>2</td>
</tr>
<tr>
<td>Other cardiac surgery</td>
<td>2</td>
</tr>
<tr>
<td>Preoperative creatinine 1.2 to 2.1 mg/dl</td>
<td>2</td>
</tr>
<tr>
<td>Preoperative creatinine &gt; 2.1</td>
<td>5</td>
</tr>
</tbody>
</table>
More recently Thakar et al have developed another clinical score to predict postoperative ARF “weighing” the effect of ARF’s major risk factors (7).

A total of 33,217 patients who underwent open-heart surgery at the Cleveland Clinic Foundation (1993 to 2002) have been studied.

The primary outcome was ARF requiring dialysis. The score was a a good predictor of ARF across all risk categories (Table 3). These results allowed to identify high-risk subgroups who could be involved in future randomized trials with the aim to identify strategies able to reduce the incidence of AKI after cardiac surgery.

PROPHYLACTIC STRATEGIES

The prophylactic strategies of the renal function preservation during the surgery traditionally emphasized two goals: 1) avoidance of nephrotoxic insult; 2) prevention or reversibility of the renal hypoperfusion supporting the renal perfusion pressure by the cardiac outcome, the arterial pressure and an adequate intra-vascular volume state (8). Renal injury in critically ill patients is worsened by contrast agents and antibiotics among others (Table 4).

Minimizing and avoiding the use of contrast agents perioperatively, especially in patients at high-risk for contrast nephropathy, helps to reduce renal injury. When possible, plasmatic nephrotoxic drugs concentrations must be measured daily.

The kidney performance is strictly bridged to the cardiac performance in fact the kidneys, although their combined weight is less than 1% of total body weigh, normally receive the 20-25% of the cardiac output (CO).

A low CO, during the surgery, decrease dramatically the renal perfusion pressure and activates a number of renal vasoconstrictor systems (sympathetic nervous system, renin angiotensyn system, and vasopres sin secretion) which damage indirectly the kidneys. Marathias et al. have shown that preoperative intravenous hydration has decreased the risk of irreversible renal damage in patients with moderate-to-severe renal insufficiency undergoing cardiac surgery regardless of the kind of fluid adopted (crystalloids or colloids) (9). Obviously, an excessive perioperative fluid load should not be administrated in order to avoid several complications such as pulmonary oedema.

Beyond an adequate CO and an intravascular volume status an optimal arterial pressure is mandatory to ensuring an adequate renal perfusion pressure. In the normal mammalian kidney, loss of autoregulation of RBF generally occurs at a mean arterial pressure (MAP) of 75-80 mmHg. There are no absolute MAP values to sustain the renal perfusion pressure in fact, a MAP of 65 mmHg could be inadequate for renal resuscitation in elderly or diabetics patients, while it could be high enough for patients without co-morbidities. A blood pressure of 60 mmHg is likely to be inadequate in every patient (10).

When the volume expansion is not sufficient to achieve these goals in ICU patients, the vasoactive drugs (many of which have inotropic and vasopressor properties) could be used. Anyway, to our knowledge no randomized controlled studies have inves-
tigated if the perfusion pressure affects the renal outcome. Recently Di Giantomasso et al. (11) in a study on animals showed that 0.4 mcg/kg/minute of norepinephrine (NE) in the normal mammalian circulation increased renal blood flow, urine output and creatinine clearance. Notably the effect of NE on the renal function was safe in patients with post-bypass hypotensive vasodilatation (12). Although further studies are needed to evaluate the effect of NE, in subjects with normal cardiac function or septic shock there are no reasons to avoid NE administration in patients with poor renal function. To date, NE remains the vasopressor of choice in hypotensive states with preserved or increased cardiac output for its efficacy in restoring the MAP.

**PHARMACOLOGICAL STRATEGIES**

**Diuretics**
The administration of loop diuretics in ARF patients is common practice in ICUs. Loop diuretics:
1) improve the tubular flow and the hydraulic pressure;
2) increase the production of vasodilating prostaglandins increasing the cyclo-oxygenases's activity;
3) reduce the efficacy of the Na–K–2Cl co-transporter (NKCC2) decreasing the sodium transport and the O2 consumption;
4) preserve the vulnerable medullary tubular segments from the ischaemic damage.

Mehta et al. showed that the use of diuretics in critically ill patients with ARF is associated with an increased risk of death and non recovery of renal function (13). The following consideration should be done:
1) the use of diuretics by converting an oliguric in a nonoliguric form could delay the recognition of ARF, the severity of the ARF and the institution of dialysis;
2) the successful conversion of oliguria to diuresis does not mean a milder form of ARF;
3) the diuretics have no impact on the patient outcome.

In a double-blind randomized controlled trial continuous infusion of furosemide has been associated with the highest rate of renal impairment in cardiac surgery patients (14). The same authors have suggested the use of mannitol to protect the renal function. In fact the mannitol:
1) induces an osmotic diuresis which prevents the tubular obstruction;
2) decrease the epithelial and endothelial cell swelling limiting the vascular congestion and tubular obstruction;
3) is a free radicals scavenger;
4) increases the synthesis of intra-renal prostaglandin generating an efficacious renal vasodilation. Sides effects are volume depletion, and an increased medullary consumption of O2. Despite of these features, a small prospective randomized clinical trial in cardiac surgery patients without previous renal impairment failed to show any significant differences in renal outcome when mannitol was administrated with prophylaxis purpose (15).

**Steroids**
In a randomized clinical trial, anti-inflammatory agents such as dexamethasone, administrated before CPB, showed no protective effect on perioperative renal dysfunction in low-risk cardiac surgical patients (16).

**Dopamine receptors agonists**
When infused in so-called “renal doses,” between 0.5 to 2 μg/kg body weight/minute, dopamine increases renal plasma flow,
GFR, and sodium excretion. In a double-blind, randomized, controlled trial, 126 patients with preoperatively normal renal function undergoing elective cardiac surgery received a continuous infusion “renal dose” dopamine (2 μg/kg/minute), furosemide (0.5 mg/kg/minute), or isotonic sodium chloride as placebo, at the beginning of surgery for 48 hours or until the discharge from the intensive care unit (14). The continuous infusion of dopamine was ineffective for renal protection and not superior to isotonic saline in preventing postoperative dysfunction. Also a larger randomized trial in early ARF has failed to show any benefit of the dopamine in preventing renal injury, renal replacement therapy, or death (17).

Fenoldopam stimulates dopamine 1 (and not dopamine 2) receptors, thus inducing, theoretically, a greater vasodilation in the renal medulla than in the cortex. Furthermore, fenoldopam has no alpha or beta adrenergic activity and as evidenced by Aravidan et al., in a rat model, fenoldopam is able to reduce the ischemic-reperfusion injury-induced inflammation involving NF-kB pathway (18). In patients at high risk of postoperative acute renal failure undergoing cardiac surgery with cardiopulmonary bypass, fenoldopam prophylaxis was an independent protective factor for postoperative renal failure within the subgroup of patients who suffered a postoperative low output syndrome (19).

On the other hand Bove et al. in a prospective single-center, randomized, double-blind trial in a cardiac surgery setting evidenced no significant difference in peak postoperative serum creatinine level, need of renal replacement therapy and intensive care unit, hospital stay, and mortality between fenoldopam and placebo group (20). Recently two interesting meta-analysis showed fenoldopam efficacy in preventing renal damage (21, 22) in critically ill patients or in those undergoing major surgery. Anyway further large multicentric randomized clinical trials are needed to justify a widespread use of fenoldopam to avoid renal impairment.

**Radical scavengers**

Because cardiopulmonary bypass and cardioplegic arrest are associated with formation of free radicals, which damage various organs particularly the kidneys, radical scavengers were hypothesized to protect the renal function.

Oxidative stress could be attenuated by N-acetylcysteine (NAC), which directly scavenges reactive oxygen species, regenerates the glutathione pool, and reduces oxidative stress during CPB. Nevertheless in a phase II, randomized, controlled trial, Haase et al. have shown that N-acetylcysteine has been no more effective than placebo in attenuating cardiopulmonary bypass-related acute renal failure in high-risk cardiac surgery patients (23).

**Arteriolar vasodilator**

Natriuretic peptides showed to cause afferent arteriolar vasodilation and efferent arteriolar vasoconstriction, thereby increasing GFR. They also block tubular re-absorption of sodium chloride, re-distribute renal medullary blood flow, disrupt TGF and reverse endothelin-induced vasoconstriction. In the NAPA trial, a prospective double-blind clinical trial, the administration of nesiritide, a recombinant human B-type natriuretic peptide, in patients undergoing CABG with CPB was associated with a better renal function and survival outcome (24). Sackner-Berneistein et al. in a recent metaanalysis on the use of the nesiritide in acutely decompensated heart failure (ADHF) showed that nesiritide significantly increases the risk of renal function impairment although the worsening renal function could reflect only hemodynamic effects and no a true renal injury (25).
Calcium channel blockers cause afferent arteriole vasodilation and natriuresis. They also reduce intracellular calcium influx and act as a free radical scavenger. In a placebo-controlled study led in patients undergoing CABG, diltiazem has increased urine output and creatinine clearances (26). However, two more recent placebo-controlled clinical trials showed no effect on renal function (27, 28).

Prostaglandins are involved in the afferent arteriole vasodilatation such as the inhibition of pro-inflammatory cytokines during cardiac surgery. A pilot study indicated that low-dose of prostacyclin could preserve the renal function in high-risk patients after coronary bypass surgery (29).

On the hypothesis that the adenosine receptors are involved in modulating intrarenal haemodynamics during ischaemia theophylline was studied with a double-blind, placebo-controlled trial in patients with normal preoperative renal function who underwent elective CABG (30). No difference in the incidence of acute renal failure has been found between cases and controls.

Clonidine has been associated with a higher creatinine clearance in two randomized double-blind trial conducted by Myles et al. and Kulka et al. (31, 32).

Optimization of renal function prior to the surgery could reduce the risk of perioperative ARF.

Durmaz et al. have performed an interesting study to assess whether correcting fluid and electrolyte abnormalities with dialysis in patients with chronic renal insufficiency prior to surgery would have reduced the incidence of post-operative ARF and mortality (33).

The study showed a significant low incidence of acute renal damage, death and a shorter length of ICU and hospital stay between the patients who received hemodilysis twice within 72 hours before the surgery and who not. However the results can not be conclusive because of a small size of patients involved into the study.

**RENEAL REPLACEMENT THERAPY**

There is no agreement on the timing and the kind of RRT in AKI. Bellomo et al. have suggested these criteria to start the RRT (34):

1. anuria or oliguria (urine output < 200 ml/12 h);
2. hyperkalemia (k > 6.5 mmol/l);
3. severe acidemia (pH < 7.1);
4. azotemia (urea > 30 mmol/l);
5. clinically significant organ edema (particularly lung);
6. uremic encephalopathy, pericarditis, or neuropathy/myopathy;
7. severe dysnatremia (Na > 160 or < 115 mmol/l);
8. hyperthermia;
9. drug overdose with a dialyzable product.

About the kind of RRT to use in ARF there are no conclusive studies. In fact, although the intermittent hemodialysis (IHD) remains the most common treatment, continuous renal replacement therapies (CRRT) and slow, low-efficiency daily dialysis (SLEDD) are becoming widely used. Each technique carries its own set of advantages and disadvantages.

**CONCLUSIONS**

In conclusion AKI is one of the most serious complications of cardiac surgery associated with increased morbidity and mortality. Ischemic injury of the kidney, exotoxins (antibiotics, anesthetic agent, contrast media, diuretics), endotoxins (myoglobin), and preexisting renal impairment are risk
factors associated to acute postoperative renal failure.
Maintenance of adequate intravascular volume perioperatively, optimization of preoperative renal function, and the avoidance of nephrotoxic medications are currently the keys to prevent perioperative AKI. Several studies on the use of pharmacological agents have failed to show any effect to prevent the perioperative AKI. Further randomized case-control studies with adequate statistical power are needed to have more conclusive data.

No conflict of interest acknowledged by the authors.

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Troponin Testing After Cardiac Surgery

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ABSTRACT

Single biomarker measurements can predict outcome after cardiac surgery. and may assist in decision making about diagnostic and therapeutic steps following surgery. Although comparative data are relatively lacking some data exist to suggest that among markers of myocardial necrosis, results from cardiac troponin (cTn) measurement may be superior for risk prediction after cardiac surgery to those from the MB isoenzyme of CK (CK-MB). Loss of cardiac troponins from necrotic myocardium is not replenished through re-expression of genes that might increase protein synthesis, and release of cTn appears to represent irreversibly damaged myocardium.

Not every cardiac surgical procedure is associated with the same degree of cTn elevation and forms of cardioprotection may importantly affect concentrations of cTn after coronary artery bypass grafting. Similarly, less cardiac injury may occur depending on the form of anesthesia used during surgery. Great caution must be exercised when utilizing cTnT or cTnI for diagnosis of post-cardiac surgery regional acute myocardial infarction: in this context clinical factors must be applied at the risk of a false diagnosis. On the other hand, concentrations of both cTnT and cTnI have repeatedly and unequivocally been shown to be prognostic for delayed recovery, intensive care unit utilization, as well as short- and longer-term mortality following cardiac surgery.

Keywords: coronary artery bypass grafting surgery, troponin, myocardial infarction.

Multiple methods exist for stratifying patient risk for complications after cardiac surgical procedures.

Including complex risk scoring systems such as the EUROSCORE (1), as well as more simple approaches such as single biomarker measurements, the ability to judge risk following potentially life-threatening open-heart procedures is of considerable importance.

The ability to accurately judge prognosis for adverse outcome not only provides important information regarding risk for the clinician to discuss with the patient both pre- and post-operatively, but also may assist in decision making about diagnostic and therapeutic steps following surgery in the context of a post-operative complication (such as detection of acute loss of bypass grafts in the setting of a coronary artery bypass graft (CABG) procedure).

Furthermore, knowledge of impending complications allows for decision making regarding intensive care unit (ICU) bed availability, as those patients predicted to have complications are more likely to have prolonged ICU lengths of stay (LOS).

As noted, options for risk assessment include accurate, albeit complicated risk scoring systems.

On the other hand, more discrete, single-measure risk tools have been examined for post-cardiac surgery risk assessment, including biomarker testing. The attractiveness of biomarker-based risk assess-
ment of patients either pre-operatively or post-operatively is intuitively attractive, as measurement of biomarkers such as natriuretic peptides, creatine kinase (CK), or the cardiac troponins (cTn) allows for an objective assessment of the underlying biology of the patient, rather than focusing on more subjective measures. Although each of these biomarkers have been shown to be predictive of risk following cardiac surgical procedures, their use is limited by a relatively poor understanding of the factors that lead to their release during and after cardiac surgery, as well as the optimal mode for their measurement and interpretation.

Although comparative data are relatively lacking with respect to the value of biomarkers for risk prediction after cardiac surgical procedures, some data exist to suggest that among markers of myocardial necrosis, results from cTn measurement may be superior for risk prediction after cardiac surgery to those from the MB isoenzyme of CK (CK-MB) (2-5). This is consistent with the superiority of cTn for diagnosis and risk stratification across the wide spectrum of cardiac syndromes. With this in mind, recent consensus guidelines have adopted measurement of serum cTn as the “gold standard” for diagnosis of myocardial injury and risk stratification in the setting of cardiovascular diseases (6). Among the situations considered in consensus guidelines for cTn use is excessive myocardial necrosis following cardiac surgery, including CABG; referred to as a “Type 5” myocardial infarction (MI), the use of cTn is endorsed in manner depicted in Table 1.

**CARDIAC TROPNON BIOLOGY**

The distribution of Tn in muscle tissue is best considered as a “two compartment” model. The contractile proteins of the myofibril contain the majority of the protein, which is a complex of three protein subunits: Tn C (the calcium-binding component; molecular mass 18 kDa), TnI (the inhibitory component; molecular mass 22.5 kDa), and TnT (the tropomyosin-binding component; molecular mass 37 kDa); the myofibril is thought to contain about 95% of the Tn present in muscle, while a smaller cytosolic component is also known to exist (7).

Although multiple Tn isoforms exist in muscle, cardiac-specific isoforms of TnT (cTnT) and TnI (cTnI) have been identified, and assays for their measurement are now widely available.

Mechanistically, the release of cTn is thought to occur whenever myocardial injury occurs, irrespectively of the mechanism. The best studied situation, of course, is acute MI from an ischemic cause; in this setting a 40-80% decrease of tissue cTnT and cTnI may be documented, which is directly reflective of release of either peptide in the peripheral blood. Furthermore, in pig hearts with severe left ventricular remodeling two months postinfarction, both cTnI and cTnT were decreased 80% and

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**Table 1 - Consensus guidelines for application of cTn testing following cardiac surgery** (6).

- For patients with normal baseline cTn values, elevations above the 99th percentile upper reference limit (essentially any measurable cTn) are indicative of peri-procedural myocardial necrosis.
- A type 5 MI is defined as:
  - Increases of cTn greater than five times the 99th percentile upper reference limit, plus
  - New pathological Q waves/new left bundle branch block or
  - Angiographically documented new graft or native coronary artery occlusion or imaging evidence of new loss of viable myocardium
40%, respectively, compared with nondiseased normal myocardium (8). These data demonstrate that loss of cardiac troponins from necrotic myocardium is not replenished through re-expression of genes that might increase protein synthesis, and release of cTn appears to represent irreversibly damaged myocardium.

Some debate exists about whether transient ischemia without cell death may lead to release of cTn from efflux of the cytosolic component, however this has not been proven, and only speculative at present. In the setting of acute ischemic injury, detectable concentrations of cTn may be found in peripheral blood within 4 hours; with the advent of higher sensitivity cTn (hsTn) methods, a change in the concentration of cTn may be found even earlier, perhaps within an hour of injury. Following acute MI, depending on the size of the infarct as well as whether revascularization occurred, peak concentrations of cTnT or cTnI tend to be seen within 24-48 hours, and fall over a period of days. It is not well known if other mechanisms of myocardial cell death lead to a different set of release kinetics. For example, unusual patterns of cTn release may be seen after endurance exercise. On the other hand, following cardiac surgery - where a multiplicity of mechanisms for cTn elevation may exist (see below) - it has been established that cTn kinetics are largely similar to that of acute MI.

cTn ELEVATION AFTER CARDIAC SURGERY: WHY DOES IT OCCUR?

It is very well-established that cTn elevation is nearly universal after cardiac surgical procedures (3, 9-12); there are multiple mechanisms proposed to explain the finding of myocardial injury after cardiac surgery: pre-operative elevation of cTn may persist into the post-operative setting, intra-operative injury may occur related to cardiac manipulation, inadequate myocardial protection, intra-operative defibrillation or acute post-bypass hemodynamic instability, while post-operative injury may be associated with acute loss of bypass grafts. In one recent study, each of these mechanisms were supported as a cause of cTnT elevation in the post-operative setting (11) (Table 2).

Not every cardiac surgical procedure is associated with the same degree of cTn elevation, an important fact to be kept in mind. In a cohort of 224 subjects undergoing a wide range of cardiac surgeries, including CABG but also valve repair or replacement, heart transplantation, ventricular

| Table 2 - Selected variables predictive of cTn concentrations after cardiac surgery. |
|---------------------------------|--------------------------------------------------|
| Effect on post-operative cTn    | |
| Age                            | ↑                                                |
| Estimated glomerular filtration rate | ↑                                              |
| Acute MI within a week of surgery | ↑                                                |
| Pre-operative need for IABP   | ↑                                                |
| Total number of distal anastomoses | ↑                                              |
| Bypass time                    | ↑                                                |
| Number of intra-operative defibrillations | ↑                                           |
| Need for placement of intra/post-operative IABP | ↑  |
| Higher core temperature during surgery | ↓                                             |
| Beating heart surgeries       | ↓                                                |
| Warm cardioplegia             | ↓                                                |
| Desflurane, sevoflurane        | ↓                                                |
| anesthesia                     |                                                  |

IABP denotes: intra-aortic balloon pump.
assist device implantation, or more minor procedures such as pericardial stripping, a wide range of cTnT values were observed (3) (Figure 1), with the higher concentrations of the marker seen in those patients that underwent coronary revascularization; this implies - supported by the data in Table 2 - that a significant percentage of circulating cTn following cardiac surgery is related to an ischemic mechanism. This is further borne out in studies of patients with excessive cTnI elevation after CABG, where a higher prevalence of acute graft loss was detected (4), as well as longer-term follow up of patients after CABG, where excessive post-operative cTnT release was associated with a higher likelihood for death and need of revascularization at one year (13), implying more complex coronary anatomy and higher risk for intra-operative ischemic necrosis. Nonetheless, the association between coronary disease and cTn after surgery is not absolute: notably, cTnT and cTnI have both been shown to be useful after pediatric cardiac surgical procedures in the absence of coronary atherosclerosis. While the association between cTn and the presence/severity of coronary artery disease (CAD) in patients undergoing CABG is necessary to keep in mind, other caveats are important to consider when measuring cTn in this setting. Firstly, while less well understood, there are certain forms of cardiac surgery associated with surprisingly high levels of cTn in the absence of CAD or obvious complications, in particular surgical maze procedures for atrial fibrillation management.

In addition and perhaps more importantly, it is also well-known that forms of cardioprotection may importantly affect concentrations of cTn after CABG, such that a wide range of release might be expected to occur depending on the form of cardio-

**Figure 1**

Concentrations of cTnT at various time points (arrival to ICU, 6-12 hours and 18-24 hours) for different forms of cardiac surgery. Of note, pericardectomy, off-pump CABG (OPCAB), and non-CABG procedures were generally associated with lower post-operative cTnT values (3).
plegia utilized. For example, those patients undergoing revascularization with cardiopulmonary bypass are expected—even in the absence of obvious complication—to have considerably higher concentrations of cTn (5, 9, 14-19). This difference in “expected” cTn might be problematic if the marker is used for post-operative risk stratification, but it turns out that in the context of complications, use of the same cTn cut-point is associated with similar prognostic value whether a patient was revascularized using on-pump (ONCAB) or off-pump (OPCAB) methods (11, 20) (see below for more details). Similarly, less cardiac injury may occur depending on the form of anesthesia used during surgery (21-28).

In recognition of the multiple reasons for cTnT or I elevation after cardiac surgery, it should not be surprising that values for these biomarkers are elevated very soon after surgery, often upon arrival to the ICU; prognostic associations will be discussed later, yet both the value of cTn on arrival to the ICU as well as later values may be prognostically meaningful. Thus, sampling at ICU arrival, as well as 18-24 hours may provide unique prognostic information (3, 11).

**cTn CONCENTRATIONS AFTER CARDIAC SURGERY: WHAT IS TRULY ABNORMAL?**

Keeping in mind the multiple reasons for elevation of cTnT or I after cardiac surgery, it should become obvious to the reader that use of these markers for diagnosis of “acute MI” after CABG is incrementally challenging. One can appreciate the efforts of consensus recommendations to incorporate other variables into the equation for definition of post-cardiac surgery MI, such as electrocardiogram (ECG) findings, documentation of bypass graft loss or imaging findings suggesting loss of myocardial function. However, associations between the presence of Q-waves or LBBB and acute graft loss following CABG are weak at best, and cTn concentrations do not clearly elevate more excessively when such ECG changes are found (11). Furthermore, coronary and graft angiography after CABG is rarely performed, and imaging studies for myocardial dysfunction are variably specific for MI.

Thus, an inevitable reliance on biomarker results for post-operative risk assessment could theoretically occur, and if misinterpreted, could lead to an excessive percentage of patients diagnosed with an “acute MI”; this becomes a particularly thorny issue when considering the cut-points endorsed by consensus guidelines, which are rather low. For example, in a recent study of patients undergoing CABG, the median cTnT was 1.08 ng/mL. Among these subjects, 99.4% had a cTnT ≥ 0.01 ng/mL (the 99th percentile concentration for a normal healthy population), and 96.6% had a cTnT ≥ 0.15 ng/mL (the consensus recommended cut-point), most often in the absence of obvious complication. Using consensus cut-points for cTn, a 100% sensitivity for post-CABG MI was observed, but this was associated with a specificity of 4.2% and a dreadfully high misclassification rate (11). Although the utility of cTn testing for secure diagnosis of regional acute MI after cardiac surgery is in question (particularly given the robust data suggesting that significant elevation of cTnT and cTnI is very common after these procedures in the absence of such a syndrome), the results of numerous analyses would argue that troponin testing after cardiac surgical procedures may add important prognostic value nonetheless. Indeed, it is now well-established that cTn concentrations following
cardiac surgery are strongly predictive of impending adverse cardiovascular events including post-cardiac surgery instability (4, 5, 12, 14, 17, 29-46), ICU length of stay (LOS) (30, 40), ICU utilization (such as duration of ventilator use and need for and number of vasopressors) (3, 11), shock, post-operative quality of life (2), and both short and longer term mortality (4, 5, 12, 14, 17, 29-46).

Interestingly, although current guidelines accept a very low upper reference limit for cTn testing after cardiac surgery, the results of numerous studies would suggest the true inflection point in cTn values for risk prediction is considerably higher (Table 3).

For example, in a prospectively gathered cohort of patients undergoing a wide range of surgical procedures, the optimal cut-point for cTnT to predict adverse outcomes was 1.58 ng/mL (3); this cut-point, more than 10 times above the currently endorsed upper reference limit for cardiac surgery, was recently validated among a larger group of more than 800 subjects undergoing CABG (11) (Table 4).

### Table 3 - Examples of recently reported optimal cTn cut-points for prediction of risk following cardiac surgery.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Cut-point</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>cTnT</td>
<td>0.46 ng/mL</td>
<td>Lehrke, et al. (36)</td>
</tr>
<tr>
<td></td>
<td>0.80 ng/mL</td>
<td>Nesher, et al. (12)</td>
</tr>
<tr>
<td></td>
<td>1.0 ng/mL</td>
<td>Brown, et al. (20)</td>
</tr>
<tr>
<td></td>
<td>1.58 ng/mL</td>
<td>Januzzi, et al. (3)</td>
</tr>
<tr>
<td></td>
<td>1.60 ng/mL</td>
<td>Mohammed, et al. (11)</td>
</tr>
<tr>
<td>cTnI</td>
<td>8.49 ng/mL</td>
<td>Croal, et al. (34)</td>
</tr>
<tr>
<td></td>
<td>13.0 ng/mL</td>
<td>Lasocki, et al. (48)</td>
</tr>
<tr>
<td></td>
<td>13.0 ng/mL</td>
<td>Papparella, et al. (18)</td>
</tr>
<tr>
<td></td>
<td>14.0 ng/mL</td>
<td>Hashemzadeh et al. (49)</td>
</tr>
<tr>
<td></td>
<td>19.0 ng/mL</td>
<td>Benoit, et al. (31)</td>
</tr>
<tr>
<td></td>
<td>23.8 ng/mL</td>
<td>Fellahi, et al. (35)</td>
</tr>
<tr>
<td></td>
<td>25.0 ng/mL</td>
<td>Immer, et al. (50)</td>
</tr>
</tbody>
</table>

*Various assays for cTnI were used in these various studies, so reference ranges may not entirely correlate.

Table 4a - Percentage of cTn elevation as a function of upper reference limit among patients undergoing CABG, including off-pump CABG (OPCAB) (11).

<table>
<thead>
<tr>
<th>cTnT cut-point</th>
<th>Value</th>
<th>Elevated, all</th>
<th>Elevated, OPCAB</th>
</tr>
</thead>
<tbody>
<tr>
<td>99th percentile for a healthy population</td>
<td>0.01 ng/mL</td>
<td>99.4%</td>
<td>96.4%</td>
</tr>
<tr>
<td>10% coefficient of variation</td>
<td>0.03 ng/mL</td>
<td>98.9%</td>
<td>84.0%</td>
</tr>
<tr>
<td>Consensus cut-point</td>
<td>0.15 ng/mL</td>
<td>96.6%</td>
<td>72.6%</td>
</tr>
<tr>
<td>Januzzi et al.</td>
<td>1.60 ng/mL</td>
<td>36.7%</td>
<td>13.1%</td>
</tr>
</tbody>
</table>

Table 4b - Performance of different potential cut-points for predicting risk following CABG.

<table>
<thead>
<tr>
<th>cTnT cut-point</th>
<th>Value</th>
<th>NPV</th>
<th>Misclassification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consensus cut-point</td>
<td>0.15 ng/mL</td>
<td>100%</td>
<td>96%</td>
</tr>
<tr>
<td>Januzzi et al.</td>
<td>1.60 ng/mL</td>
<td>99%</td>
<td>28%</td>
</tr>
</tbody>
</table>

Importantly, in a multivariable logistic regression model adjusted for the Society for Thoracic Surgery risk score, cTnT values significantly predicted early post-operative complications of death (OR=3.20; 95% CI=1.5-6.9; \( P = .003 \)), death/heart failure (OR=2.04; 95% CI=1.2-3.5; \( P = .008 \)), death/vasopressor need (OR=2.70; 95% CI=2.0-3.6; \( P < .001 \)), and the triple composite of death/heart failure/vasopressor need (OR=2.57; 95% CI=1.9-3.4; \( P < .001 \)) (11), results similar to those from Simon et al (41).

This suggests that excessive cTn release after surgery adds to the prognostic merit of an already complex risk stratification model and should be considered an independent predictor of bad outcomes independent of other variables considered in this setting.
SPECIAL CIRCUMSTANCES: CARDIAC OPERATIONS WHERE cTn VALUES ARE LOW

As noted, cTn values are nearly universally elevated among those patients who undergo cardiac surgical procedures, but this is not entirely the case. In a very small percentage of patients, normal or even unmeasurable cTn values may be observed. As already demonstrated in Figure 1, a wide range of cTn values are observed after cardiac surgical procedures, largely dependent on the use of cardiopulmonary bypass as well as the presence and extent of CAD. Accordingly, those patients who are expected to have the lowest concentrations of cTn after cardiac surgery include those patients who undergo non-bypass, beating heart surgeries, such as pericardectomy. Interestingly, even in the presence of CAD, when beating heart, off-pump CABG (OPCAB) is utilized for revascularization, cTn concentrations are considerably lower than in on-pump CABG (CABG) patients (Figure 2) (11, 15-20). This naturally has raised concerns about whether the same cTn cut-points could be used for both ON-CAB and OPCAB patients. Fortunately, it would appear that despite concentrations of cTn are lower in OPCAB patients in general, in the context of a complication, values for cTn are similar to ONCAB patients with complications (11, 20), and when cut at similar levels as for ONCAB patients (e.g. 10-15 times the upper reference limit), the marker has comparable negative predictive value (91-97%) for excluding complications, irrespective of cardioprotection strategy (11).

Figure 2
Off-pump CABG (OPCAB) is typically associated with lower median concentrations of cTn than in patients operated on the pump (ONCAB). Nonetheless, the prognostic value of cTn is preserved in OPCAB patients, using the same cut-points as ONCAB patients (11).

4.00
3.00
2.00
1.00
0.00
0.00

P<.001

Peak cTnT (ng/mL)

OPCAB (N=84) ONCAB (N=764)

cTn TESTING: POTENTIAL FUTURE APPLICATIONS

In addition to being adopted in a more widespread fashion simply for post-cardiac surgical risk stratification, cTn testing in this setting may have other logical applications in the future. For example, with more widely available non-invasive imaging options such as computed tomography angiography, an elevated cTn might trigger early graft angiography to ensure patency (4, 46); such an approach has been suggested to be of value to “save” potentially th-
threatened grafts in the early post-operative period (47). Furthermore, given the clear association between \(cTn\) concentrations and cardioprotection, it is quite clear that these markers may be considered as a surrogate endpoint for the value of novel cardioplegia agents, as well as other forms of intra-operative myocardial protection strategies (21-28).

**cTn TESTING AFTER CARDIAC SURGERY: SUMMARY AND LOGICAL APPLICATION**

Based on the available data in the literature, \(cTnT\) and \(cTnI\) are superior to CK-MB as a biomarker for post-cardiac surgery patient evaluation. Elevation in both \(cTnT\) and \(cTnI\) is expected nearly universally after cardiac surgery, particularly in ONCAB patients, and those undergoing CABG with associated valve replacement surgery. These elevations are due to multiple causes, including presenting syndromes, intra-operative management and post-operative events.

Given the multiplicity of causes for \(cTn\) elevation after cardiac surgery, and the particular rarity of a regional MI, in this context, the use of \(cTnT\) or \(cTnI\) for the diagnosis of regional MI after cardiac surgery is problematic. Furthermore, consensus recommended cut-points for diagnosis of the so-called “Type 5” MI are so low as to render the application of \(cTnT\) and \(cTnI\) quite problematic, given the expected over-reliance on objective measures - such as biomarkers - for the diagnostic evaluation of the post-operative patient, in whom other means for evaluation (such as ECG or echocardiography) are either non-specific or not easily delivered/interpreted in the ICU setting. Thus, great caution must be exercised when utilizing \(cTnT\) or \(cTnI\) for diagnosis of post-cardiac surgery regio-

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J.L. Januzzi

32.


Carotid Endarterectomy: experience in 8743 cases

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ABSTRACT

Introduction: Recently published case series of patients undergoing carotid endarterectomy suggested a reduction in the rate of perioperative neurologic events when compared to those reported in the large randomized trials performed in the 1990s, without great differences between high and low risk patients.

Methods: As a major center of Vascular Surgery we prospectively collected data on 8743 carotid endarterectomy procedures (eversion technique 75%, patch closure 17.5%) performed in the period 1992-2009.

Results: Perioperative mortality was 0.32% (27/8743) with myocardial infarction being the most frequent cause (9 patients). Perioperative neurological morbidity was 1.04% (91/8743) with 51 major and 40 minor strokes. In 201 cases (2.3%) a cervical hematoma (suture-line bleeding in 41 cases and or diffuse oozing in 160 cases) in the early postoperative period necessitated urgent wound revision. In 262 (3.0%) cases we observed permanent or transient lesions of cranial nerves in the postoperative period. There was no significant difference in the combined ipsilateral stroke and perioperative death rate in octogenarian patients (2.1% in octogenarians and 1.2% in younger patients, p > 0.05), even though an increasing trend was evident.

Conclusions: Carotid endarterectomy has a reduced rate of perioperative complications when compared to those previously reported in literature. The low complication rate is related to improved preoperative patients evaluation, surgeons' increasing experience and to surgical and anesthesiological techniques. Carotid angioplasty and stenting should have their results compared to these real world results of carotid endarterectomy in order to assess their reliability when treating extracranial cerebrovascular disease.

Keywords: vascular surgery, carotid endarterectomy, stroke survival anesthesia.

INTRODUCTION

In the early 1990’s several well designed randomized studies clearly demonstrated the effectiveness of carotid endarterectomy (CE) over best medical therapy alone for symptomatic and asymptomatic patients with a significant stenosis of the internal carotid artery (ICA) (1-6).

More recently, published case series of patients undergoing CE (7-10) assessed a more conclusive reduction in rate of perioperative complications (neurologic events) compared to risk/benefit ratio reported in the former trials (1-6), without great differences between high- and low- risk selected patients.

In this article we report our experience as a major center of Vascular Surgery, performing 8743 CE procedures in the period 1992-2009, and we show our results analysis with evaluation of perioperative complication rates.

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METHODS

From 1992 to 2009, we performed a total of 8743 CE, on 6468 patients, with a mean age of 69.3 years (range 32-92).

Clinical characteristics and age distribution are presented in Table 1 and Graph 1.

Neurological history was positive for stroke in 1224 (14%) and for transient ischemic attack (TIA) in 2798 patients (32%). In 4721 cases (54%) patients were neurologically asymptomatic or presented non specific symptoms (Graph 2).

Our current clinical protocol and the percentage of adherence to it in this case series are described below.

Indications

According to well-defined guidelines, established in 1998 during the Consensus Conference of the American Heart Association (11, 12) and endorsed by the Italian Society

**Table 1 - Clinical characteristics of 6468 patients who underwent 8743 carotid endarterectomy procedures in the period 1992-2009 in our centre.**

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>5764 (69%)</td>
</tr>
<tr>
<td>Age, mean (years)</td>
<td>69</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1176 (14%)</td>
</tr>
<tr>
<td>TIA</td>
<td>2689 (32%)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>4538 (54%)</td>
</tr>
<tr>
<td>Risk Factors</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>5579 (66%)</td>
</tr>
<tr>
<td>Dislipidemia</td>
<td>3966 (47%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1664 (20%)</td>
</tr>
<tr>
<td>Smoke</td>
<td>3975 (47%)</td>
</tr>
<tr>
<td>Positive TC</td>
<td>5151 (61%)</td>
</tr>
</tbody>
</table>

**Graph 2**

Neurologic medical history of 6468 patients who underwent 8743 carotid endarterectomy procedures in the period 1992-2009 in our centre.
Carotid Endarterectomy: experience in 8743 cases

of Vascular Surgery (13), symptomatic and asymptomatic patients with carotid stenosis > 60% are judged eligible for CE, depending on life expectancy, comorbidities, general condition and surgical risk (which must be less than 3% for asymptomatic patients and less than 6% for symptomatic patients).

Elderly patients are not excluded from surgical treatment on the basis of age alone (10.1% of octogenarians in our series), as, even in this subgroup of patients, CE may be a safe mean of stroke prevention, provided that patients receive adequate selection (14-16).

Indication and timing of urgent carotid revascularization in presence of acute neurological symptoms still represent a much debated issue, even though some investigators advocate good results with emergent surgery in highly selected patient (17-19). In our series we had 157/8743 cases (1.8%) of urgent carotid revascularization, performed for two specific conditions: patients with crescendo TIAs and a single TIA with ulcerated plaque (136 cases); patients developing post-operative cerebral ischemia (21 cases), respectively.

Preoperative hospital stay and diagnostic work-up

Although patients could be ideally admitted to hospital the same day of surgery (20), we usually prefer to admit the patient 1 day before surgery.

Duplex Scanning: duplex scanning (i.e. an ultrasonography study characterized by the combination of B-scan imaging and Doppler imaging) performed at a validated laboratory has almost completely replaced angiography (21-24). When the results of a duplex scan are uncertain, magnetic resonance angiography (MRA)/computed tomography angiography (CTA) represent our second choice while contrast angiography with arterial catheterization (stroke rate of 1.2% in ACAS trial) (6) is our last choice.

Cerebral Parenchymal Study/Neurological Auditing: as far as cerebral parenchymal imaging is concerned, preoperative computed tomography (CT) scan is useful to show previous ischemic cerebral lesions with prognostic significance for new strokes after CE (25). CT may also reveal the presence of aneurysms, vascular malformations, and brain tumors.

In the last 2 years, preoperative cerebral CT was performed in 87% of our patients, especially those showing high risk features (neurologic symptoms, bilateral stenosis, high risk plaque). Magnetic resonance imaging (MRI) is performed only in selected cases (5.8%).

Cardiac Status: the most important non-neurologic area to explore preoperatively is cardiac status. As a matter of fact, most of perioperative complications and deaths are cardiac in origin (26). There is no consensus on optimal cardiovascular preoperative evaluation before CE. Some studies suggest that routine scintigraphic or ultrasonographic tests are useful in detecting patients at high risk (27, 28), but there is no evidence of cost-effectiveness of this approach.

According to our current protocol, echocardiography with dobutamine test is performed in patients with a history of cardiac disease or with a pathologic electrocardiogram (EKG) (16%).

Preoperative Medication: given the benefit of antiplatelet therapy in patient undergoing CE without a substantial higher risk of bleeding (29) we discontinue acetylsalicylic acid/ticlopidine only the day of operation, while low molecular weight heparin at low doses is administered overnight.

Surgical procedure

Anesthesia: the choice of the anesthetic management for carotid surgery is still controversial. A recent large randomized trial
showed no differences between general and locoregional anesthesia (30) in clinically relevant endpoints. Nevertheless, minor advantages of locoregional anesthesia (LRA) are well recognized. It can be performed outside the operating room with adequate patient monitoring, and allows a less cumbersome neurological monitoring during clamping. Some authors also described better hemodynamic stability during surgery and improved postoperative pain control with the use of LRA (31). Performing LRA in recovery room before entering the operating room helped us to save at least 30 min on the use of the operating room, compared to general anesthesia. Currently LRA is used in most cases of our series (96.3%) (Graph 3).

The choice between superficial or deep cervical plexus block is performed by the attending anesthesiologist, taking into account his/her experience in the technique and patients’ characteristics (e.g. double antiplatelet therapy). Superficial cervical plexus blocks is performed by a 20 G needle, introduced into the skin at the midpoint of the posterior border of the sternocleidomastoid muscle in a slightly caudal direction, and 0.75% ropivacaine (≈5 ml) is injected along the posterior border in cranial and caudal directions subcutaneously, superficial and deep to the fascia of the muscle. An injection in a fan-like fashion is also performed subcutaneously from the posterior border of sternocleidomastoid toward the midline of the neck. Deep cervical plexus block is performed at C2-C3-C4 level. A 20 G needle is inserted in the skin until it reaches the transverse process of the corresponding vertebra and then anesthetic is injected after an accurate suction-test. We generally administer 5 ml of 0.75% ropivacaine for each injection. The total amount of ropivacaine used is 1.5 mg/kg (considering both the superficial and the deep cervical block). The last step of the procedure is the infiltration of the incision line with 10 to 15 ml of lidocaine 1%. Subsequent sensory loss to a pin-prick in the C2-4 dermatome distribution is recorded. Additional lidocaine (1%) is administered intraoperatively by surgeons in 1 ml aliquots (either superficially into skin and subcutaneous tissues or deep into and around the carotid sheath), as required when the patient reported discomfort. It should be useful to add a mild intravenous injection of opiates (Fentanyl 1ug/kg or Remifentanyl 0.025-0.05 ug/kg/min), to reduce discomfort associated to the forced posture during

Graph 3
The increase in the use of Loco Regional Anesthesia in our centre in the study period to perform 8743 carotid endarterectomy procedures.
Carotid Endarterectomy: experience in 8743 cases

surgery. We feel very comfortable with use of lidocaine and ropivacaine, as the former ensues a rapid onset of pain control while the latter, with its long lasting nerve block (5-8 hours), guarantees good analgesia in the early postoperative period.

Heparinization: systemic heparinization is routinely used (a dose of 70 IU/kg was used until '04 when we reduced the dose to 50 IU/kg in order to minimize the risk of cerebral haemorrhage). Activated Clotting Time (ACT) is measured before and after heparin administration, with a target ACT greater than 200”. Protamine is administered in half the dose required to antagonize all heparin.

Surgery

Exposure of the carotid bifurcation: exposure starts with incision of the skin right on the anterior border of the sternocleidomastoid muscle. Depending on the characteristic of the neck, our standard incision usually was 10-15 cm long. Recently we have started to reduce the length of the skin incision by mapping the location of the carotid bifurcation at the time duplex is performed (Figure 1). Once the bifurcation is freed from the surrounding structures, we progress to mobilization of the arteries. Special care is mandatory to avoid damage to the vagus nerve. The internal carotid artery (ICA) is then mobilized to a point distal to the visible atheromatous lesion. The ICA is dissected along its edge, starting at the upper end of the bulb. During dissection is important to avoid the X and XII cranial nerves. As we use eversion as our routine technique, we routinely dissect the ICA distally in order to have a secure end-point. The surgical technique used in each single case is chosen according to carotid anatomy and cerebral tolerance to cross-clamping.

Standard endarterectomy: once the component of the carotid bifurcation are dissected and heparin administered, the arteries are

Figure 1
Our currently used shorter incision (5-7 cm long).

Figure 2
Complete clamping of the carotid bifurcation.

Figure 3
Arteriotomy of the bifurcation (two suture lines are placed to help maintaining the bifurcation open).
clamped with microsurgical clamps. We usually clamp the ICA first, then the CCA and finally the ECA. If the superior thyroid artery has to be clamped, we usually deal with it using a mini-bulldog clamp (Figure 2). We always perform a tolerance test of 1 minute before starting with the CE. Arteriotomy extends over the last 2 centimeters of CCA and into the ICA to a point beyond the termination of the plaque (Figure 3). The plane for endarterectomy is sought at the level of the bulb, where the plaque is usually most developed. The proximal endpoint of the plaque, at the level of the CCA, is usually obtained by direct cutting. The ICA endarterectomy is the most important part. The plaque is therefore pulled along its axis, paying attention not to stay close to the artery wall, while the ICA is pushed the opposite way. The remaining surface is then accurately debrided using forceps. Finally we proceed to closure of the arteriotomy with a synthetic patch (Figure 4). We have currently abandoned direct closure, as a recent metaanalysis has shown a higher rate of restenosis, compared to patch closure or eversion (33).

Eversion technique: eversion allows optimal correction of elongated ICAs either by shortening the ICA after endarterectomy or by reimplanting the ICA a little further down into the CCA (34). The suture line is basically an end to side anastomosis that does not produce diameter reduction. This technique is expeditious and straightforward and it is the most used in our series (75% of cases). One drawback is that occasionally it does not allow a clear-cut view of the distal endpoint of the endarterectomy, thus requiring systematic intraoperative arteriography as a quality check. Once clamping of the ICA, CCA and ECA is established and the patient responds well to neurologic evaluation (of at least 1 minute), the ICA is transected at its origin (Figure 5). ICA endarterectomy is carried out by eversion in
cranial direction (Figure 6). Careful flushing of the ICA and the CCA is performed before reimplanting of the ICA (Figure 7). At the end of the reimplantation an intraoperative arteriography is performed in order to exclude a distal intimal flap in the ICA which could lead to dissection or thrombosis (Figure 8).

Shunting: we are used to perform selective shunting with a Javid shunt (10.7%). On declamping we perform the Imparato maneuver in order to minimize the ischemic time (Figure 9).

Intraoperative quality check: to reduce the incidence of complications related to technical defects after CE, several types of quality control tests have been employed by different authors (35,36). Angiography through direct puncture of the CCA is probably the simplest and most direct way to show technical defects in the endarterectomized ICA. In our series, intraoperative completion arteriography is used routinely for eversion endarterectomy and only in dubious cases for other techniques. Selective carotid arteriography is performed through direct puncture of the CCA. If angiography shows a substantial defect of the distal end-point, the surgical options include resection and bypass grafting or a longitudinal incision on the internal carotid artery, with fixation of the intimal flap with tacking sutures and patch closure. Intraoperative carotid artery stenting (CAS) has emerged as a valuable
alternative in the management of perioperative technical complications following CE (Figure 10). Currently stenting of the distal flap through direct cannulation of the CCA is often performed in case of a technical defect detected intraoperatively (Figure 11).

**Post-operative management**
In our experience selective postoperative ICU stay was necessary only in 1.5% of cases. This result is related to the high-quality nursing in the surgical ward, to the presence of a surgeon on call 24 hr/day, and to the availability of accurate, noninvasive monitoring at the patient’s bedside.

**Bleeding:** in spite of meticulous hemostasis and cautious administration of heparin, postoperative bleeding is relatively frequent, particularly for patients on double antiplatelet therapy (37-39). The amount of tolerable bleeding in the neck is reduced by anatomic limitations related to the fasciae and the risk of airways’ compression makes cervical hematoma a surgical emergency. When orotracheal intubation is required, it is important to remember that this may be extremely difficult to carry out because of the hematoma and swelling of the soft tissues that may limit the view of the larynx and the passage of the tube. Therefore intubation should be performed with a fibroscope. If the patient is breathing well, we perform hemostasis under local anesthesia. If the patient is intubated and there is large swelling of the soft tissues, we prefer to leave the tube in for at least 24 hr, along with steroid administration and head elevation.

**Discharge:** because the surgical procedure has a rather low local invasivity, safe discharge from the hospital may be as early as the first postoperative day (40). On the first postoperative morning, the surgeon inspects the wound and remove the drain. An independent neurologist rechecks the neurological status. If the patient is stable from a cardiovascular and neurologic standpoint, the EKG is unchanged, and the patient has no fever, has a dry wound without any neck swelling, and can eat, void, and ambulate spontaneously, discharge from the hospital can be scheduled for the same day. In our series patients are discharged at a mean of 2.5±0.8 postoperative days.

**Follow-up/Restenosis**
The patient is seen at the outpatient clinic on postoperative day 10 to remove the skin staples. If the patient is living far from the Hospital, he/she spends 1 more day in hospital and is asked to stay in town for a few days after the procedure. Follow-up duplex
scan is scheduled after 3, 6 and 12 months and then on a yearly basis. Patients living in Lombardia have a 93% clinical and duplex scan follow-up. For patients not living in Lombardia follow-up rate is lower but still acceptable (62%).

RESULTS

The eversion technique was used in 6558 cases (75%). CE with patch closure (we used Dacron patches until 2001 then we turned to polyurethane patches) was used in 1530 cases (17.5%) and direct suture, now abandoned, in 655 cases (7.5%) (Graph 4). A Javid shunt was selectively used in 935 cases (10.7%) because of the presence of clinical and instrumental (modification of the EEG pattern) signs of cerebral ischemia. Shunting was twice as common in case of contralateral occlusion. Mean use of the operating room was 74 min. Through systematic use of locoregional anesthesia (LRA), our use of the operating room is at least 30 min less than that we have during general anesthesia. Mean clamping time accounted for 14 minutes in case of patch closure and for 10 minutes in case of eversion endarterectomy. Perioperative mortality was 0.32% (27/8743), with myocardial infarction being the most frequent cause (9 patients). Other causes of death were: ischemic stroke (7 patients), hemorrhagic stroke (7 patients), respiratory failure caused by cervical hematoma (1 patient), wound infection (1 patient) and suture failure with massive bleeding (2 patients). Perioperative neurological morbidity was 1.04% (91/8743). Of these 91 cases 51 (56%) were major strokes and 40 (44%) minor strokes, with complete or near complete resolution of all symptoms.

A total of 201 cases (2.3%) developed cervical hematoma in the early postoperative period, which necessitated urgent wound revision. Of these, 8 patients had the wound emergently reopened in the surgical ward because of progressive airway compression, which was fatal in one case. The cause of hematoma was either suture-line bleeding (41 cases) or diffuse oozing (160 cases).

In 262 (3.0%) cases we observed permanent or transient lesions of cranial nerves in the postoperative period, with the recurrent laryngeal nerve involved in 135 cases (51.7%), the hypoglossal in 67 (25.8%), the facial in 27 (10.3%), the glossopharyngeal in 21 (7.5%) and the accessory in 12 cases (4.7%). We registered 25 cases of wound infection. All were readmitted to hospital and treated with surgical drainage. In case of patch closure (13 patients), the patch was removed and replaced with a saphenous vein one. In all cases except one, who suffered fatal stroke, recovery was unevent-
ful. Elderly patients (i.e., octogenarians) face an increased operative risk (41). Since 1995 we performed 883 CE in octogenarians. The 1-year mortality was significantly higher among the octogenarians (1.37% vs. 0.32%, chi-square test, p<0.05), however, there was no significant difference in the combined ipsilateral stroke and perioperative death rate (2.1% in the octogenarians and 1.2% in younger patients, p>0.05), even though an increasing trend was evident. At the time of first admission 21.3% of patients presented with bilateral carotid stenosis greater than 70% and underwent staged bilateral CE. After the first intervention we experienced a rate of combined ipsilateral stroke and perioperative death rate of 2.1% in the octogenarians and 1.2% in younger patients, p>0.05), even though an increasing trend was evident. At the time of first admission 21.3% of patients presented with bilateral carotid stenosis greater than 70% and underwent staged bilateral CE. After the first intervention we experienced a rate of combined ipsilateral stroke and perioperative death rate of 2.1%, comparable to those experienced in normal patients. Similarly, the rate of combined ipsilateral stroke and perioperative death after the second operation was 1.3%. It is noteworthy that there was a significantly greater need for shunting if the second operation was performed early, especially within 30 days from the first one (42). Contralateral occlusion was present in 18.2% of the patients. The rate of combined ipsilateral stroke and perioperative death rate was 1.37% in this subgroup. Complication rate did not differ from that of other patients, the only difference being a double rate of shunt insertion in patients with contralateral occlusion (43). In 431 cases (5%) we observed a >50% restenosis that was treated only if symptomatic or critical ≥80% (44), either with PTA-Stenting (71 cases; 0.8%) or surgically (32 cases; 0.3%). In 32 cases we performed redo open procedures (Figure 12) with 6 cases (18.7%) of cranial nerve injuries, and a combined ipsilateral stroke and perioperative death rate of 6%.

DISCUSSION

Carotid endarterectomy is safe and effective for stroke prevention in significant symptomatic and asymptomatic carotid stenosis. Writing the word “carotid endarterectomy” on the browser of any service that include English citations from MEDLINE and other life science journals for biomedical articles, each one of us can easily notice than over 9000 papers on CE have been published in peer-reviewed journals from 1953, and, incredibly, until nowadays, the surgical indications, the choice of neurological monitoring, the anesthetic management, and the surgical technique are still controversial. Moreover, in the last decade, carotid artery angioplasty and stenting (CAS) gained popularity as an alternative to carotid endarterectomy (CE), particularly in high risk patients, being less invasive and potentially minimizing the risks of wound complications and cranial nerve injury, which may translate into shorter length of hospitaliz
tion and less resource utilization. Waiting for future developments, CAS is at present an effective treatment, particularly appealing in high-risk patients with significant carotid artery stenosis, however, there is no real evidence that CAS provides better results in the prevention of stroke compared to CE. We currently limit its use in cases of restenosis, in patients unfit for surgery, and for the perioperative correction of distal flaps after CE that may be difficult to treat surgically.

Our results of 8743 CEs demonstrate a progressive reduction in the incidence of complications, which can be compared to that reported by the major international studies of the last few years. This reduction is related to improved preoperative patients evaluation, surgeons’ increasing experience, and to surgical and anesthesiological technique developments.

In terms of surgical technique, good results have been reported for all commonly used surgical techniques. We prefer to adopt a flexible approach choosing surgical technique on the basis of intraoperative findings and the need for shunt insertion. Shunt use has become less frequent, reflecting better neurologic monitoring and shorter clamping times.

Limitations
Our study entails some limits. First of all the intrinsic limit of being a retrospective study, with all the bias due to its design. Moreover, in the first years, only major adverse cerebrovascular events were recorded, whereas TIA or non fatal myocardial infarction were not labeled as complications. This has led without any doubt to an under-estimation of the total rate of complication of CEA, even if it is still a topic of discussion what the real importance of this minor complications might be.

One second major limit is the fact that the short in-hospital stay of these patients (2.5 days) might make a discrete amount of postoperative complications, in particular those cardiac in origin, to go unnoticed. It is in fact well documented in literature that, on average, cardiac complications happen 2 to 4 days after the surgical stress has occurred. This might then lead to underestimate the total incidence of MI in the postoperative period, as many of our patients come from areas outside of our district.

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Solving the Challenges of Large Multicenter Trials in Anesthesia

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ABSTRACT
This paper describes many of the challenges encountered when establishing a large multicentre trial in cardiac anesthesia. We address funding, authorship, multisite ethics review, patient recruitment, data quality management, communication with individual sites, and strategies to enhance cooperation and patient recruitment.

Keywords: cardiac anesthesia, anesthesia, multicenter trials, methodology.

INTRODUCTION
Large randomized controlled trials, testing new treatments in routine clinical practice, can optimize generalizability and so are clinically relevant and reliable (1). They thus provide the best evidence of effectiveness (2, 3). Most large trials are multicenter studies, and often conducted in many countries. Despite being labelled as “simple” or “pragmatic” trials (1, 3, 4), reflecting their focus on easy-to-administer treatments in routine settings, they create a number of difficult challenges for those involved. However the rewards are great and include the opportunity to answer important clinical questions reliably, to publish in top-ranked journals, and to be recognized by your peers. We would like to share our experience of establishing a large multicenter trial testing two interventions in coronary artery surgery (5). The aspirin and tranexamic acid for coronary artery surgery (ATACAS) trial is a factorial designed trial in 4600 patients, designed to detect thrombotic (principally myocardial infarction (MI), stroke, and death) and bleeding complications – see www.atacas.org.au. We reasoned that although aspirin may increase bleeding, there is some evidence that it could reduce thrombotic complications after coronary artery surgery. The opposite can be said for antifibrinolytic therapy. In both cases there are insufficient randomized trials to address these questions unequivocally. A large multicenter trial is required (5). Pharmaceutical companies are unlikely to fund such research, and so specialty or government research bodies must provide financial support.

PROTOCOL DEVELOPMENT AND PLANNED SUB-STUDIES
The effort and commitment to undertake or contribute to a large multicenter trial
is substantial. Before embarking on such a project, the aims and study hypothesis should be clearly outlined, hopefully addressing a clinically important question. A supportive literature review will provide a background and justification for conducting such a trial. There are often opportunities to design small sub-studies at selected centres, requiring additional data collection, increasing opportunities for authorship and additional publications. The explanatory data can be used to link the effects of an intervention to selected intermediate outcomes that may correlate with the main study aims. For the ATACAS trial we are conducting substudies to investigate aspirin non-responsiveness in a subset of our study population, perioperative genomics with the iPEGASUS group, and the effects of tranexamic acid on seizure risk.

The study protocol describes the science of the research project, and the study procedures manual the structure and processes that allow it to be properly conducted.

**STUDY MANAGEMENT**

Experienced trial management and leadership are vital for successful large scale clinical trials. Numerous individual centers, sometimes with their own research interests and studies, must arrive at a consensus regarding study procedures and data collection, inclusion of other clinicians (not just anaesthesiologists) and language and cultural differences, all of which test goodwill and cooperation on a multinational scale. Trials should have a core group of co-investigators responsible for the overall management and running of the trial, headed by a Principal Investigator (PI). The PI, co-investigators, and perhaps other experts, constitute the trial steering group. Some bodies recommend that the chairman of the trial steering committee should not otherwise be involved in the trial (6). The trial steering committee should meet at regular intervals throughout the life of the trial to discuss overall management, progress and policy decisions. Trial management includes data management, data security and back-up, quality checks, review of patient safety and including consideration of reports from the trials’ data and safety monitoring board. Each individual site reports via the study chief investigators to the steering committee. Ideally each site should have a lead investigator who takes responsibility for overseeing the study at their site, for which they should be acknowledged in the final publication. Financial management should be continually assessed throughout the trial (7).

**FUNDING**

Large trials require substantial funding. The ATACAS trial is primarily funded by the Australian National Health and Medical Research Council (NHMRC). Being government provided, such funding is usually limited, and when considering the costs and demands on clinicians and research staff, it is usually insufficient to properly fund all aspects of the trial. Most centers have other cardiothoracic research projects which may compete for patients, research staff availability, and interest from local clinicians. There may be competition with pharmaceutical company-funded projects which typically provide much higher rates of remuneration (8, 9). The ATACAS trial is an investigator-initiated trial, funding individual sites Australian Dollars (AUD) 700 (about Euro 390) per patient enrolled; we have been involved in some pharmaceutical company-funded studies providing funds at 5-10 times that rate.

Large clinical trials aim to address clinically important questions, often testing simple inexpensive interventions. There is a compelling
argument that such trials ought to be funded by the health (not medical research) budget because of the opportunities to immediately improve outcomes of healthcare (1, 10).

**PROCUREMENT OF STUDY DRUG**

Initial management hurdles can include sourcing of study drug and matched placebo, and these issues can vary across countries because of differences in the status of the study drug licensing. For ATACAS, we approached the pharmaceutical companies that produce aspirin and tranexamic acid to assist with free supply of study drug and matched placebo.

For aspirin, this proved to be relatively straightforward and positive, but for tranexamic acid it resulted in a two year delay and eventual disappointment. We subsequently arranged our own purchase of tranexamic acid from the UK, leaving us with the cost-burden for supply of this drug to most ATACAS sites around the world. This of course also delayed the commencement of the trial.

Following public announcement of the results of the BART trial (11), and the market withdrawal of aprotinin around the world (12), the initial purchase price of tranexamic acid went from AUD30 (about €17) per box to AUD100 overnight. This added a new and unexpected cost burden to the study.

Fortunately this did not interrupt recruitment although it highlights how trial budgets can suddenly be tested.

**GOVERNANCE**

Before enrolling participants in a clinical trial individual sites must gain approval by their hospital’s institutional review board or ethics committee (13).

Another mandatory step is informed consent (14), for which local expectations and requirements can vary, as well as sometimes introducing a need for translation of such documents.

The timeline for this process from beginning (initial contact with site) to end (management receiving the approval letter) averages six months. This is a major barrier for many sites who may otherwise be interested in collaboration (15).

**AUTHORSHIP AGREEMENT**

Researchers are rated according to the quality and quantity of their publication record. Large trials involve many individuals, but only some deserve authorship on the main publication(s). Others may share in authorship of subsidiary publications. In any case, all of those involved in the conduct of a large trial should be acknowledged, and this is typically published as an appendix to the main publications.

For this reason acknowledged site leaders ought to be given credit for their leading role within their own institutions. Authorship is a vexed topic, and it cannot be overstated: who and under what circumstances each collaborator is included in the authorship or acknowledgement lists must be outlined at the beginning of the trial, and ideally a signed authorship agreement be completed in order to avoid disappointment and conflict.

**INDEMNITY**

Multicenter trials should have a clinical trial agreement (CTA) signed with each individual site. This pertains to both pharmaceutical-sponsored and investigator-initiated trials.

The CTA document requires legal review
and comment from each site. This adds cost and poses another potential for delaying start up of the trial. Pharmaceutical-sponsored trials have the resources to provide their own indemnity insurance, but investigator-initiated trials rarely can because such funding is not included in most research funding bodies’ budgets.

In such cases it is usual to ask that individual sites cover their own indemnity costs, because the study procedures usually only involve currently established therapies. As we, and others (10), argue, investigator-initiated large pragmatic trials ought to be considered “public good” research and so individual institutions should support such trials.

SITE SELECTION

Site selection is vital to a successful trial. It relies on some research infrastructure and staffing, to identify eligible patients for recruitment, study interventions and follow-up (16).

Initial site investigators invited to join the ATACAS trial were those previously involved in other multicenter trials (17-20), and have proven track records. All sites were asked to discuss the feasibility of undertaking the trial with their respective cardiothoracic surgical colleagues. Support from the surgeons at each institution was an essential component for the trial. New sites were also sought.

Publicity for the trial occurred via presentation at scientific meetings, establishment of a trial website (www.atacas.org.au), and journal publication (5). Rahbari et al (21) challenge the surgical community to optimize study power using properly conducted, pragmatic (multicenter) trials with large sample sizes. Variation in surgical practice, surgical skill and surgeon preference have proven to be obstacles to large multicenter trials in surgery (8), but Devereaux et al. (22) have suggested solutions.

RESEARCH NURSES/COORDINATORS AND PATIENT RECRUITMENT

It is very important that the infrastructure and staff to conduct research at each site are actively sought, available and most importantly supported (23-26). Sites that have limited infrastructure in place to conduct research must commence with recruitment of a research nurse or coordinator, and this takes time (recruitment, training). The coordinating center for the trial can assist in this regard.

Constant communication and availability of assistance has proved to be important in facilitating this role. The research nurse is responsible for the screening, recruitment, consent, data collection, data storage, subject logs, data entry, and protection of human subjects in clinical trials (Figure 1) (27).

It is vital that the research nurse be supported by the site investigator, and participating units (28), as this will be the main contributing factor to the success or failure of patient recruitment (25). It has been previously reported that the individual undertaking the recruitment can influence recruiting patients to the trial (29). No difference was found when doctors or research nurses were examined, but there was a statistically significant difference when recruitment was undertaken by the operating surgeon (29). This therefore highlights the importance of having the support from all disciplines involved in the research.

A recent survey of trials published in the Lancet or BMJ found that nearly 60% of
trials had either failed their recruitment target or required an extension of their planned recruitment period (29). Recruitment of participants to trials is one of the most important aspects to a successful trial (23, 24, 30). It has long been recognized that recruitment is a much greater problem than is perceived by the investigator when instigating and designing the trial (8, 24). During the course of the trial it is important to implement and identify strategies to overcome barriers to recruitment (31). Delays in recruitment lead to important scientific answers being left unanswered, increased unidentified costs, early closure of trial (8, 23-25, 30, 31), statistical power may be reduced (29, 31), poor morale (16), and delayed uptake into clinical practice.

Studies have shown that individual site training and regular feedback and communication to staff improve recruitment rates (15, 32). Start-up meetings, personalised education and training visits assist in improving recruitment (29). The management team provide the following process to assist with site recruitment (Figure 2).

Newsletters are used to disseminate information to all sites and focus on recruitment techniques, addressing frequently asked questions, current and new sites, future meetings, changes to the database and recently published literature relevant to the study.

**DATA MANAGEMENT AND MONITORING**

Data collection from multiple sites, in various time zones, needs to be streamlined and secure.

For the ATACAS trial we use paper-based case report forms (CRF) at each centre, and the data are later transferred onto a web-based form. The online data entry is accessed through a password-protected link on the trial website.

The site also offers a trial summary, recruit-
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The web-based database therefore allows for the original study CRf to be retained at each site for audit and privacy purposes, as well as reducing the time spent in identifying and resolving data queries, and minimizing data entry errors. This has been identified as one factor that may assist in increasing efficiency (29). We believe simple study procedures encourage participation in multicentre trials. Careful monitoring of the recruitment process throughout studies is vital, and enables the management center to identify problem areas at individual sites (25).

These logs can be sent to the data management center on a monthly basis and tabulated for review by the steering committee. If a site has a lag in recruitment, the research manager or project officer can initiate communication with the site to assist in identifying areas requiring assistance. Correct and complete study procedures can be checked, including consent, secure data storage, and verification of trial events.

CONCLUSIONS

Large multicenter clinical trials are demanding but ultimately rewarding in that they provide reliable answers to everyday clinical problems. Clear guidelines on all aspects of the trial procedures assist in a teamwork approach to overcoming the many barriers to successful completion of such trial.
No conflict of interest acknowledged by the authors.

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Infusione tramite via venosa periferica di fenoldopam mediante pompa elastomerica

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ABSTRACT

Introduction - Fenoldopam has been used to protect renal function in critically ill patients and in those undergoing major surgery, where a possible damage of kidney is expected. Numerous randomized studies and meta-analysis demonstrated the efficacy of fenoldopam in this setting. We performed this study to demonstrate the feasibility of administering fenoldopam, through an elastomeric pump connected to a peripheral vein, to patients undergoing nephron sparing surgery.

Materials and Methods - Twenty consecutive patients, ASA physical status class I-III, undergoing laparoscopic or laparotomic renal tumorectomy were enrolled. Fenoldopam was infused through an elastomeric pump at a fixed dosage of 0.1 mcg/kg/min, obtained after diluting the drug with saline solution according to the weight of the patient. We injected the drug through a peripheral vein from the induction of anaesthesia for 48 hours after the end of surgery.

Results - The infusion of fenoldopam did not modify the haemodynamic parameters. We did not find episodes of hypotension and only in three patients we registered episodes of tachycardia, not requiring the suspension of the infusion. No other side-effect was noted.

Conclusion - The administration of fenoldopam, through an elastomeric pump, in patients undergoing renal tumorectomy is feasible through a peripheral vein access

Keywords: fenoldopam, acute renal failure, elastomeric pump, peripheral vein, kidney.

INTRODUZIONE

L’insufficienza renale perioperatoria costituisce un importante fattore determinante il prolungamento della degenza ospedaliera e un incremento della mortalità e della morbilità.

Il ruolo del fenoldopam come agente nefroprotettore è già stato suggerito in diverse situazioni nelle quali è possibile il realizzarsi di un deterioramento della funzione renale, come ad esempio, la chirurgia vascolare e cardiaca (1-4). Due recenti meta-analisi hanno mostrato come il fenoldopam riduca la necessità di trattamento dialitico renale e incida positivamente sulla mortalità sia in pazienti “critically ill” (5) che in quelli sottoposti a chirurgia cardiovascolare (6).

Il fenoldopam è un dopamino agonista che esplica la sua azione selettivamente a livello dei recettori adrenergici DA1, la sua azione è quasi nulla o trascurabile a livello dei recettori DA2. Il recettore DA1 è localizzato a livello postsinaptico sul muscolo liscio renale, cardiaco, mesenterico e cerebrale, a livello renale il recettore è situato nel tubulo prossimale, nella midollare e nella corticale. Pertanto il fenoldopam è in grado di aumentare il flusso ematico renale e la
infusione tramite via venosa periferica di fenoldopam

filtrazione glomerulare senza che si verifichi aumento della frequenza cardiaca o comparsa di tachiaritmie come può accadere con la dopamina. Il Fenoldopam esplica il suo effetto ipotensivo attraverso un decremento delle resistenze vascolari periferiche ed è approssimativamente sei volte più potente della dopamina nel produrre vasodilatazione renale. La natriuresi e la diuresi possono avvenire senza vasodilatazione, ciò sta ad indicare un sito d’azione a livello del tubulo renale prossimale. Gli effetti benefici del fenoldopam possono essere correlati ad un’altra proprietà del farmaco (ancora in studio), quale un effetto anti-infiammatorio descritto da Aravindan et al. (7).

In chirurgia urologica, oggi, sempre più spesso rispetto al passato, si preferisce in caso di neoplasie renali effettuare, quando possibile, un approccio conservativo effettuando interventi di tumorectomia o crioterapia renale in alternativa alla nefrectomia radicale. Numerosi studi hanno infatti dimostrato che vi è un rischio significativamente aumentato di nuova insorgenza di IRC in pazienti sottoposti a nefrectomia radicale rispetto a quelli sottoposti a nefrectomia parziale (8). Gli interventi di tumorectomia renale, siano essi laparotomici o laparoscopici, comportano un periodo di clamaggio dell’arteria renale e impongono all’anestesista la messa in atto di tutte le strategie nefroprotettive disponibili. La nefroprotezione è ancora più importante in pazienti monorene (su base congenita o chirurgica) o con insufficienza renale cronica (IRC). Al fine di prevenire il danno ischemico renale è necessario mantenere anzitutto un’ottimale volemia, inoltre si è soliti far ricorso a farmaci quali mannitol, furosemide o dopamina a dosaggio renale sebbene non vi sia alcuna evidenza scientifica sulla loro efficacia.

Dal momento che i migliori benefici del fenoldopam sono stati ottenuti per somministrazioni prolungate, ci siamo proposti di validare la sicurezza e l’efficacia di un sistema di infusione continua del fenoldopam che a differenza delle comuni pompe infusionali di uso intensivistico, fosse gestibile con maggiore facilità e sicurezza anche in un reparto chirurgico. Abbiamo scelto di utilizzare elastomeri a velocità fissa per infondere fenoldopam al dosaggio fisso di 0.1 gamma/kg/min in via venosa periferica, avviando l’infusione del farmaco subito dopo l’induzione dell’anestesia e proseguendola per le 48 h successive.

METODI

Nel nostro servizio di urologia presso la struttura Ospedale San Raffaele - Ville Turro vengono eseguiti circa 300 interventi annui di tumorectomia renale; quando possibile è privilegiata la tecnica laparoscopica o robotica.

L’intervento di tumorectomia renale prevede il clamaggio dell’arteria renale con una fase di ischemia calda il cui tempo massimo di sicurezza per evitare il danno renale dovrebbe essere di 30 minuti.

Nel caso in cui si preveda un tempo di clamaggio più lungo, il chirurgo provvede ad effettuare un’ischemia fredda portando la temperatura renale al di sotto di 20°.

Sono stati inclusi nello studio 20 pazienti consecutivi classe ASA 1-3 candidati ad interventi di tumorectomia renale mono o bilaterale condotti per via laparoscopica o laparotomica. Sono stati considerati criteri di esclusione gravi patologie cardiache (gravi deficit valvolari e coronarici), polmonari ed epatiche.

Dopo essere giunti nel blocco operatorio sono stati posizionati ai pazienti due accessi venosi di grosso calibro su cui si è avviata un’infusione di cristalloidi. Il monitoraggio in sala operatoria prevedeva la valutazione dell’ECG, della pressione arteriosa non cruenta, della pulsiossimetria periferica e
T. Quaranta, et al.

della diuresi. L’induzione dell’anestesia è avvenuta tramite somministrazione di tio-pentone sodico 5-7 ml/kg, atracurium 0.5 mg/kg, fenatnyl 2 mcg/kg.

Il mantenimento dell’anestesia è stato conseguito con l’erogazione di gas anestetico alogenato (sevoflurane o desflurane).

L’infusione di fenoldopam è avvenuta tramite pompa elastomerica ad un dosaggio fisso di 0.1 mcg/kg/min ottenuta attraverso una diluizione in soluzione fisiologica calcolata sulla base del peso del paziente (Tabella 1).

La somministrazione del farmaco è avvenuta tramite cannula venosa periferica subito dopo l’induzione dell’anestesia e il posizionamento del paziente ed è proseguita per 48 dopo il termine dell’intervento.

Si è mantenuta una perfusione di cristalloidi (6-8 ml/kg) e colloidi (3-4 ml/kg) mantenendo una PAM > 60 mmHg (se PAM < 60 mmHg per più di 10 min era prevista la sospensione del farmaco).

Durante l’intervento è avvenuto un monitoraggio ogni 15 minuti dei valori di frequenza cardiaca, pressione arteriosa non cruenta (sistolica, diastolica e media), saturimetria e diuresi.

Gli stessi parametri sono stati valutati nell’immediato post-operatorio ed in prima e seconda giornata con un intervallo di 2 ore. Sono state inoltre eseguite valutazioni dei valori di creatininemia sierica, creatinina clearance, potassiemia, sodiemia e calceemia nel giorno dell’intervento ed in prima e seconda giornata post-operatoria. Abbiamo anche ricercato la presenza di eventuali effetti collaterali connessi al possibile utilizzo del farmaco (Tabella 2).

Per ogni paziente si è poi proceduto alla valutazione del danno renale sulla base della classificazione RIFLE (Tabella 3).

Tabella 1 - Schema di diluizione in soluzione fisiologica di una fiala di fenoldopam in funzione del peso corporeo del paziente.

<table>
<thead>
<tr>
<th>Peso kg</th>
<th>Diluizione ml fisiologica</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>166,5</td>
</tr>
<tr>
<td>45</td>
<td>148</td>
</tr>
<tr>
<td>50</td>
<td>133</td>
</tr>
<tr>
<td>55</td>
<td>121</td>
</tr>
<tr>
<td>60</td>
<td>111,0</td>
</tr>
<tr>
<td>65</td>
<td>102,5</td>
</tr>
<tr>
<td>70</td>
<td>95,0</td>
</tr>
<tr>
<td>75</td>
<td>88,5</td>
</tr>
<tr>
<td>80</td>
<td>83</td>
</tr>
<tr>
<td>85</td>
<td>78</td>
</tr>
<tr>
<td>90</td>
<td>74</td>
</tr>
<tr>
<td>95</td>
<td>70</td>
</tr>
<tr>
<td>100</td>
<td>67</td>
</tr>
</tbody>
</table>

Formula
gamma/ml = 0,1 gamma/kg/min x Peso x60
velocità infusione 2 ml/h

Tabella 2 - Effetti collaterali prevedibili in seguito a somministrazione di fenoldopam con rispettiva incidenza nel gruppo di pazienti analizzati.

<table>
<thead>
<tr>
<th>Effetti collaterali</th>
<th>Pazienti</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Ipotensione</td>
<td>0</td>
</tr>
<tr>
<td>2 Tachicardia</td>
<td>3</td>
</tr>
<tr>
<td>3 Cefalea</td>
<td>0</td>
</tr>
<tr>
<td>4 Necessità dialisi</td>
<td>0</td>
</tr>
<tr>
<td>5 Arrossamento cutaneo</td>
<td>0</td>
</tr>
<tr>
<td>6 Ipokaliemia</td>
<td>0</td>
</tr>
<tr>
<td>7 Aritmie</td>
<td>0</td>
</tr>
<tr>
<td>8 Vomito</td>
<td>0</td>
</tr>
<tr>
<td>9 Vertigine</td>
<td>0</td>
</tr>
<tr>
<td>10 Crampi arti inferiori</td>
<td>0</td>
</tr>
<tr>
<td>11 Congestione nasale</td>
<td>0</td>
</tr>
<tr>
<td>12 Sindrome vaso-vagale</td>
<td>0</td>
</tr>
<tr>
<td>13 Fatica</td>
<td>0</td>
</tr>
<tr>
<td>14 Calo visivo</td>
<td>0</td>
</tr>
<tr>
<td>15 Dolori toracici aspecifici</td>
<td>0</td>
</tr>
<tr>
<td>16 Palpitazioni</td>
<td>0</td>
</tr>
</tbody>
</table>

Tabella 3 - Schema di diluizione in soluzione fisiologica di una fiala di fenoldopam in funzione del peso corporeo del paziente.
**RISULTATI**

In nessuno dei 20 pazienti è stato necessario sospendere l’infusione di fenoldopam per insorgenza di ipotensione o di effetti collaterali. I 20 pazienti partecipanti allo studio (14 maschi, 6 femmine) sono stati sottoposti ad interventi di tumorectomia renale laparotomica (13) o laparoscopica (7). In tre casi la tumorectomia è stata bilaterale. Otto pazienti erano affetti da ipertensione arteriosa, quattro da diabete mellito, due da insufficienza renale cronica e tre risultavano essere monoreni ad inizio procedura.

I pazienti presentavano un’età media di 62±9 anni, un peso di 80±15,3 kg, un’altezza media 172±6,4 cm. Il tempo di calmaragio e di ischemia renale è stato in media di 33±18,6 minuti.

I parametri emodinamici sono rimasti stabili durante tutta l’infusione di fenoldopam. Non sono stati registrati episodi di ipotensione e soltanto in tre pazienti si sono verificati episodi di tachicardia non grave e non richiedente la sospensione del farmaco. Non sono stati registrati altri effetti collaterali (Tabella 2).

La diuresi è rimasta valida in tutti i pazienti durante la giornata dell’intervento e nelle prime due giornate post-operatorie. Soltanto in tre pazienti (o monorene o sottoposti a tumorectomia e a clampaggio bilaterale) è stato necessario stimolarla con furosemide.

In giornata 0 la diuresi media nelle 24 h è stata di 1,6±0,7 ml/kg/h, in giornata 1= 1,5±0,7 ml/kg/h ed in giornata 2= 1,5±0,6 ml/kg/h. Si è assistito ad un incremento dei valori di creatininemia che si sono poi normalizzati entro la quinta giornata post-operatoria.

Abbiamo poi valutato la classificazione RIFLE per i diversi pazienti (Tabella 3). È importante sottolineare come i due pazienti in classe F (failure) siano rispettivamente un paziente monorene ed uno sottoposto a tumorectomia bilaterale.

**DISCUSSIONE**

Questo studio ha dimostrato, per la prima volta, la fattibilità della somministrazione per lunghi periodi del fenoldopam per via periferica e senza necessità di utilizzare una pompa siringa connessa ad una presa di corrente. Dal momento che il farmaco ha mostrato le sue migliori proprietà quando somministrato per lungo tempo, questa tecnica di somministrazione è particolarmente appetibile per i malati con o a rischio di insufficienza renale perioperatoria o periprocedurale che non hanno un accesso venoso centrale. Nella nostra casistica di 20 malati non sono stati osservati effetti collaterali (ipotensione) o problemi tecnici tali da indurre l’interruzione della somministrazione di fenoldopam postope-
Agenti farmacologici quali il mannitolo, la furosemide o la dopamina a dosaggio renale incrementano il flusso ematico renale ma non sono efficaci nel prevenire o trattare l’insufficienza renale acuta. Il fenoldopam è un agonista selettivo dei recettori dopaminergici DA1; in questo modo attraverso la sua azione riesce a determinare una vasodilatazione renale senza provocare tachicardie o aritmie come può accadere con la dopamina.

Recenti meta-analisi hanno dimostrato la sua efficacia nel ridurre mortalità e mortalità in pazienti candidati ad interventi di chirurgia cardiovascolare o “critically ill”. La review sistematica della letteratura ha mostrato come l’utilizzo del fenoldopam sia associato ad una minore permanenza in terapia intensiva oltre che ad una minore mortalità intraospedaliera in pazienti sottoposti ad intervento cardiovascolare (6).

La somministrazione di fenoldopam tramite pompa elastomerica in pazienti candidati ad interventi di tumorectomia renale risultà sicura e di facile esecuzione.
REFERENCES


The target journal: choosing the right place to submit your paper

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After having written a wonderful paper, full of interesting ideas, fascinating data and exhaustive statistics you make a terrible mistake: you send it to the wrong journal. What does ‘the wrong journal’ mean? For many it would be a journal with an unsatisfactory impact factor.
In my opinion, it is a journal where you will not have any interested readers.
Impact factor is, of course, crucial as it looks good on your CV and can earn you research funds, but citation will only occur, at least in most cases, when you are read with interest by fellow professionals from your own specific field of biomedicine.
Choosing the right place to submit your paper is therefore the first thing you have to do, even before you actually start bashing it out on your computer keyboard.
You might feel that your paper is of fundamental importance to the biomedical community, but it is always a good idea to be realistic and aim for a journal that is within your reach.
What I mean is, if you are convinced of the quality and importance of your paper, and also feel that it could be of interest to a particular group of readers, then by all means submit it to a high-impact-factor journal. For example, who wouldn’t like to be published in the New England Journal of Medicine? What you have to remember is that the NEJM receives around 4,000 papers a year yet only has the chance to publish around 450 of them.
The selection process is extremely severe, therefore, and your paper really does have to be out-of-the-ordinary and of extreme relevance to the journal’s reading population to even begin going through the peer-review process.
Submitting a paper that is even slightly below this level would mean immediate rejection (NEJM normally rejects within one week when they are not interested), so think carefully about where you decide to send your manuscript.
In any case, the destination of your paper is known as the target journal.
As I said at the beginning, your target journal does not necessarily need to have a high impact factor, but must guarantee you a reading population.
The next thing to remember is that you can only send your paper to one journal at a time.
Stick to your specialty and even try contacting the Editor via e-mail before submit-
The target journal: choosing the right place to submit your paper

ting your paper to find out whether or not he will consider publishing it, based on its subject matter. This can save you time, sometimes a lot of time.
When you have chosen the journal be sure to follow its Instructions to Authors.
Although more than 500 journals use the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/), also known as the Vancouver Document, each journal will also have its own set of rules and regulations.
Specific requirements might include:

- the use of double spacing throughout the text
- the necessity to use the standard IMRAD (Introduction, Methods, Results And Discussion) format
- the sequence to be used: title page - abstract - key words and abbreviations - text - acknowledgements - references - tables and figures - legends

So, remember:
- choose a journal that is relevant to your specialty to guarantee you an audience
- choose the target journal realistically as you can only submit your work to one journal at a time: inevitable rejection means delayed publication
- get in touch with the editor of your target journal beforehand to see whether your work might be of interest or not

Finally, if you are convinced that your paper deserves to be published in the NEJM then don’t worry about the 90% rejection rate and send it to them as your target journal. He who dares sometimes wins. There's no harm in trying.

“Questo è il terzo di una serie di articoli sull’argomento. Potete indirizzare domande (in italiano o in inglese) a michael.john@hsr.it e vedrete le risposte pubblicate su questa rubrica.”

‘This is the third of a series of articles on this topic. Send any questions to michael.john@hsr.it who will answer them as part of this column.’
Questions from the readers

1. Should numbers be written as words or numbers at the beginning of sentences?

The rule is that in a biomedical manuscript single-digit numbers (1-9) have to be written as words, except when indicating units of measurement, but all other two or more digit numbers should be written as numbers. However, when the sentence begins with a number, whatever the number of digits involved, you should always write it in words.

2. What is the correct spelling for compound numbers in English: with or without a hyphen?

In the literature all compound numbers are hyphenated (e.g. twenty-five patients were enrolled).

3. Is it possible to use the present perfect form (have been) in a biomedical manuscript?

No. At times, the present perfect tense is unavoidable: e.g. when you are speaking of past events where time is not defined. However, a biomedical manuscript reports a procedure, therefore you should ALWAYS use the simple past (and simple tenses in general) throughout even when time is not specified.

4. Is it better to use the active or passive voice in medical English?

Active. Many people mistakenly feel that the passive voice is 'more scientific' than the active voice. Indeed, some journals might specify their preference for the passive and, at times, use of the passive is unavoidable and even necessary. However, the active voice is clearer, simpler and improves the flow of the written text. Avoid the passive. Be active!
L'ecocardiografia transesofagea (TEE) ormai fa parte del monitoraggio standard del paziente sottoposto a chirurgia cardiaca, e fornisce molte informazioni anche riguardo al paziente ricoverato in Terapia Intensiva. Nonostante la scelta di testi sull'argomento sia vasta, abbiamo accolto con molto piacere (e con un po' di orgoglio italiano - vedi fig. 12.1 di *Ecocardiografia transesofagea in area critica*) il libro del Dr Fabio Guarracino, Primario di Anestesia e Rianimazione CardioToracica dell'Azienda Ospedaliera Universitaria Pisana e Presidente di ITACTA (Italian Association of CardioThoracic Anesthesia), che mette a disposizione di tutti la sua esperienza nel campo dell'ecocardiografia transesofagea. La lettura del capitolato 1 “Fisica degli ultrasuoni e formazione dell’immagine” (argomento tabù della maggior parte dei medici che si interessano di ecocardiografia), illude chi spera di acquisire quelle nozioni che, a detta di molti, sono fondamentali per un buon esame ecocardiografico: la fisica dei suoni, pur essendo trattata in maniera chiara, avrebbe meritato più spazio.

Il 2° capitolo elenca le principali indicazioni e le (poche) controindicazioni all’ecocardiografia transesofagea, le precauzioni per l’uso e la cura della sonda transesofagea. Quindi nel 3° capitolo, il Dr Guarracino ci spiega passo passo i movimenti possibili della sonda e, secondo le indicazioni dell’American Society of Echocardiography e della Society of Cardiovascular Anesthesiologists, le proiezioni fondamentali per un corretto esame TEE.

Finalmente nel 4° capitolo, si entra nel vivo dell’argomento, con lo studio del ventricolo sinistro e della sua funzione, le varie metodiche di studio ed i limiti di quest’ultime. Il 5° capitolo è dedicato allo studio del ventricolo destro, che troppo spesso viene dimenticato, e invece in *Ecocardiografia transesofagea in area critica* trova il suo giusto spazio. Il 6° capitolo esplora in modo approfondito la funzione diastolica, partendo da richiami di fisiologia, fino all’impatto clinico delle valutazioni, trattando tutte le metodiche ecocardiografiche, dallo studio del flusso transmitralico alla velocità di propagazione, al doppler tissutale.

Si arriva quindi ai capitolato dedicati allo studio delle valvole, aortica (cap. 7) e mitrale (cap. 8). Soprattutto per quanto riguarda la mitrale, la trattazione è approfondita e spende molte pagine sulla classificazione anatomica e funzionale, permettendo quindi al lettore di comprendere con facilità i vari meccanismi dell’insufficienza. Da segnalare che, come da linee guida American College of Cardiology/American Heart Association del 2006, viene raccomandata la necessità della valutazione intraoperatoria della valvola mitrale dopo chirurgia riparativa, da parte di un medico formato in TEE, a prescindere dalla sua specialità. In virtù di questa precisazione, ci saremmo aspettati di trovare qualche pagina sulla valutazione delle valvole cardiache dopo chirurgia. Il capitolo 9° riveste una grande importanza, in quanto esplora la patologia dell’aorta, nel quale il TEE è l’esame di scelta per porre...
diagnosi di molte gravi lesione aortiche. Nel capitolo 10° e 11° vengono studiate in dettaglio le patologie del pericardio e le masse cardiache.

Inizia quindi una serie di 4 capitoli dedicati al rianimatore. Capitoli dedicati al trauma toracico, alla sepsi, al cuore polmonare acuto e allo shock e alla rianimazione cardio-polmonare. Sono argomenti che, spesso tralasciati da altri libri, possono invece rivelarsi molto utili. Chiude il libro un capitolo dedicato alle equazioni fondamentali che si utilizzano (spesso inconsapevolmente) durante un esame ecocardiografico.

La trattazione dei vari argomenti non si limita alla teoria pura, ma in ogni capitolo il Dottor Guarracino integra le varie metodiche con delle considerazioni cliniche e decisionali. Molto utili le indicazioni pratiche per ogni misurazione (“come si misura”): sembra di avere accanto qualcuno che, passo passo, ti spiega come eseguire le varie misure. È un peccato che le tavole fuori testo, così utili, siano così piccole; si fa fatica a interpretarle bene. Di fronte ad una scelta molto ampia di testi, manuali e atlanti, finalmente possiamo contare su di un libro scritto da un anestesista-rianimatore e dedicato a chi lavora in area critica, dalla sala operatoria alla terapia intensiva al pronto soccorso, completo e al tempo stesso chiaro.

Dr. Paolo Prati
Dr. Michele Oppizzi
How to prepare a manuscript for submission to
HSR Proceedings in Intensive Care and Cardiovascular Anesthesia

Articles in English or in Italian will be considered. The abstract should always be in English.

Manuscripts must be double-spaced on A4 pages. A margin of at least 3 cm should be provided on all sides. All type should be 12 points in size. Pages must be numbered. Word limits are not imposed on any manuscript types, but all papers should be as concise as possible.

Please send your manuscript to sussani.lara@hsr.it. The Editorial Office will send by e-mail to the corresponding author all communications related to the status of a submission, including the final decision and the scheduled date of publication.

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MANUSCRIPT
Our preferred file type for new manuscript submissions is a single Microsoft Word Doc with all figures embedded in the same document. In the manuscript, provide the title of the paper on the first page (TITLE PAGE); the title should be concise. Also list the name of each author, including the first name, and the highest graduate degree; the department and institutional affiliation of each author; and the name, address, telephone number, fax number, and e-mail address of the author to whom correspondence should be addressed. ABSTRACT. Provide an abstract of not more than 250 words. If possible, it should consist of four paragraphs, labelled Background, Methods, Results, and Discussion. They should briefly describe, respectively, the problem being addressed in the study, how the study was performed, the salient results, and what the authors conclude from the results. The manuscript itself should be possibly divided into 4 sections: Introduction, Methods, Results, and Discussion. REFERENCES. Please refrain from using automatic reference list software because its features are often lost during the publication process. Simply insert the reference number in parentheses in the text and type the reference list. References must be numbered with Arabic numerals, and cited in the text in numerical order. The reference list at the end of the article must also be in numerical order. The list headed “REFERENCES” should begin on a new page of the main text document and be double-spaced. Abbreviations for titles of medical periodicals must conform to those used in Index Medicus (http://www.nlm.nih.gov/tsd/serials/lji.html). References to abstracts, supplements, and letters to editors must be identified as such. Inclusive page numbers of references are required.

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