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The Use of Perioperative Beta-blocker Therapy

By Luc Lanthier and Matthieu Touchette

More than two million Canadians undergo surgery each year in Canada. Patients who have surgery are increasingly older and have several medical problems. It is estimated that between 1% and 5% of these patients will develop major cardiac complications, at an annual cost of about \$2 billion. Since the publication of the D.T. Mangano Study in 1996 and the consensus from the American College of Physicians in 1997, beta-blockers have increasingly become the agents of choice to reduce the risk of perioperative cardiac complications. But what are they exactly?

Perioperative Beta-blockers: A Brief History

The use of beta-blockers in perioperative care gained attention in 1996 when the Mangano Study was published in the *New England Journal of Medicine*. In this study, 200 patients with, or at risk for, coronary disease underwent noncardiac surgery and were administered atenolol or placebo for seven days. After two years of follow-up, 23 of the subjects randomized to beta-blockers had died (10%), compared to 13 patients in the placebo group (21%; $p = 0.021$, NNT = 9). Unfortunately, this study was not perfect. The patients who died during their hospitalization (four were taking atenolol and two were taking placebo) were not included in this analysis; if the analysis were to be redone based on treatment, the results would not be significant anymore ($p = 0.07$). Two patients were lost during the follow-up. Furthermore, patients taking beta-blockers were eligible to be included in the study and then had to be taken off their beta-blockers during the preoperative phase. Angiotensin conversion enzyme (ACE) inhibitors were also used more in the atenolol group from the start ($p = 0.003$).

The Poldermans Study in 1998 boosted the appeal of beta-blockers for this indication. In this study, which was also published in the *New England Journal of Medicine*, 173 patients scheduled to have vascular surgery and with an abnormal

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Perioperative Beta-blockers

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dobutamine echocardiogram (of the 1,351 patients assessed) were randomized to receive either bisoprolol or “standard” treatment. After 30 days, 18 patients from the control (standard treatment) group (34%) had died or had suffered a myocardial infarction, compared to two (3.4%) from the bisoprolol group ($p < 0.001$, NNT = 3), bringing the study to a premature halt. Unfortunately, the study was not blinded and the side effects of the treatment were not mentioned. The patient selection process was very stringent, limiting the degree to which the results can be generalized. Furthermore, the control group had a very high rate of cardiac complications. There is also a risk of having overestimated the efficacy of the treatment because of the premature termination of the study (after only 20 events). Therefore, a relative risk reduction of 90% on the 30th day of beta-blocker treatment seems almost too good to be true, especially when we know that beta-blockers administered to patients with an acute infarction (another stressful situation in itself) reduce mortality rate by approximately 25%.

New Data Questions Adequacy of Perioperative Beta-blockade

Following publication of these two studies, the popularity of perioperative beta-blockers continued to grow. Nonetheless, this practice was challenged in 2004. The Metoprolol After Vascular Surgery (MAVS) study, presented at the Congress of the Canadian Anesthesiologists' Society in 2004, evaluated the impact of metoprolol in 497 subjects who underwent vascular surgery. In this study, 25 of the 247 patients randomized to metoprolol presented

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Cardiovascular Impact of Nocturnal Hemodialysis

by Christopher T. Chan

Cardiovascular (CV) events are the leading cause of morbidity and mortality in patients with end-stage renal disease (ESRD). The etiology of CV pathology in ESRD is complex, involving ongoing myocardial injury compounded by volume and pressure overload, endothelial dysfunction and progressive arteriopathy secondary to uremia complications such as secondary hyperparathyroidism and hyperphosphatemia.

Hypertension and elevated arterial stiffness are increasingly recognized as important risk factors in uremic populations. Conventional hemodialysis (CHD; three times per week for four hours per session) only delivers 10% to 15% of renal function in an unphysiological intermittent mode. Because it occurs nightly, and is sustained over a longer dialysis time, the uremic clearance provided by nocturnal hemodialysis (NHD; five to six sessions per week for six to eight hours per session) far exceeds that of CHD. This article reviews the mechanisms underlying dialysis-associated hypertension and describes the impact of NHD on the CV system.

Clinical Problem: **Hypertension in** **ESRD Patients**

Elevation in arterial pressure in uremia may be caused by expansion of extracellular volume in a stiff arterial bed, an increase in total peripheral resistance, or a combination of these factors.

Volume Overload: **Sodium and Water Retention**

Elevated extracellular fluid (ECF) volume has consistently been found in hypertensive ESRD patients and contributes to increases in left ventricular (LV) dimensions, stroke volume, end-diastolic pressure and LV hypertrophy. Volume removal by renal replacement therapy lowers blood pressure

Conventional hemodialysis (CHD) only delivers 10% to 15% of renal function in an unphysiological intermittent mode. Because it occurs nightly, and is sustained over a longer dialysis time, the uremic clearance provided by nocturnal hemodialysis (NHD) far exceeds that of CHD.

(BP). In individuals with a failing heart, a decrease in ventricular preload may improve LV filling and stroke volume due to diastolic ventricular interaction.

Pressure Overload: **Hypertension and** **Increased Arterial Stiffness**

Elevations in systolic and pulse pressure reflect pressure overload, resulting from cardiac factors (e.g., stroke volume) and vascular factors (e.g., increased peripheral resistance and arterial stiffness). Although pathogenesis remains undefined, arteriosclerosis and increased arterial stiffness are likely major determinants. Increases in systolic, pulse pressure and arterial stiffness are independent risk factors for the development of LV hypertrophy and CV

mortality in ESRD, reflecting the importance of pressure overload in the pathogenesis of CV dysfunction in uremia.

Assessment of Arterial Stiffness

Distensibility of the arterial tree in humans can be estimated in a variety of ways, from pressure-volume curves using vascular ultrasound, pulse wave

velocity or, more recently, magnetic resonance imaging to determine the ratio of left ventricular stroke volume to brachial artery pulse pressure. In longitudinal studies, this ratio has predicted coronary heart disease mortality in elderly men.

Impact of Elevated **Arterial Stiffness in ESRD**

Increased arterial stiffness is a feature common to ESRD patients receiving CHD, and relates strongly to LV hypertrophy as well as all-cause mortality. BP reduction without concurrent improvement in arterial compliance does not alter CV event rates. Greater arterial stiffness in ESRD has been attributed to structural and dynamic factors (including uremia, hypertension, increased tissue and circulating vasoconstrictors, and



reduced nitric-oxide synthesis or bioavailability), leading to endothelial dysfunction and poorly-controlled hyperparathyroidism, promoting arterial calcification. We have shown that improvement in phosphate balance, or an increase in nitric-oxide synthesis or bioavailability, can result in greater arterial compliance. It is important to note that NHD, unlike CHD, reverses many of the abnormalities of ESRD.

Arterial and Ventricular Adaptations of Nocturnal Hemodialysis

In contrast to the effects of CHD, we have demonstrated regression of LV hypertrophy along with superior BP control following NHD. We studied 28 patients undergoing NHD for a

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minimum of two years and compared these patients to 13 self-care CHD patients. We assessed BP, ECF volume and left ventricular mass index (LVMI) before and after conversion from CHD to NHD. Systolic BP was reduced from 145 ± 20 mmHg to 122 ± 13 mmHg, ($p < 0.001$) and diastolic BP from 84 ± 15 mmHg to 74 ± 12 mmHg ($p = 0.02$) despite the withdrawal of vasoactive medications (from 1.8 per patient to 0.3 per patient; $p < 0.05$). LVMI decreased from 147 ± 42 g/m² to 114 ± 40 g/m² ($p = 0.004$). ECF volume was not reduced after conversion from CHD to NHD, suggesting that the achieved cardiac improvement occurred via mechanisms other than enhanced volume removal.

In another study of 18 consecutive patients converted from conventional to nocturnal home hemodialysis, we found that, as the dialysis dose per session (Kt/V) increased after two months, mean arterial pressure decreased from 102 ± 3 mmHg to 90 ± 2 mmHg. There was an associated decrease in calculated total peripheral resistance (from $1,967 \pm 235$ to $1,499 \pm 191$ dyn.s.cm⁻⁵; $p < 0.01$) and plasma norepinephrine levels (from 2.66 ± 0.4 nmol/L to 1.96 ± 0.2 nmol/L; $p = 0.04$). During CHD, endothelium-dependent vasodilation could not be elicited, but this was restored after a two-month period of NHD. In addition, brachial artery responsiveness to nitroglycerin improved (from $6.9\% \pm 2.8\%$ to $15.7\% \pm 1.6\%$; $p < 0.05$). Of note, no significant change in weight

and, by corollary, extracellular volume was demonstrated.

Impaired neural control of heart rate, elevated arterial stiffness and hypertension are probably central in the development of high CV mortality rates in ESRD patients. We hypothesized that NHD would increase arterial baroreflex sensitivity (BRS) for heart rate changes of hypertensive ESRD patients through an afferent vascular mechanism. Ten consecutive hypertensive ESRD patients (aged 42 ± 4 years) receiving CHD were studied before and two months after conversion to NHD. Regression slopes relating RR interval responses to increases or decreases in systolic BP were averaged to derive spontaneous BRS for each patient's heart

rate. The stroke volume/pulse pressure (SV/PP) ratio was used to estimate total arterial compliance. NHD lowered systolic BP from 143 ± 4 mmHg to 120 ± 6 mmHg ($p = 0.001$). Both BRS (from 4.76 ± 1.1 ms/mmHg to 6.91 ± 1.1 ms/mmHg; $p = 0.04$) and total arterial compliance (from 0.98 ± 0.13 ml/mmHg to 1.43 ± 0.2 ml/mmHg; $p = 0.02$) were higher following conversion to NHD. Increases in BRS correlated with increases in the SV/PP ratio ($r = 0.845$; $p = 0.002$). These findings are consistent with the concept that NHD increases BRS via greater afferent baroreceptor responsiveness to pulsatile vascular pressure.

CV disease is the leading cause of mortality in ESRD patients. A randomized controlled trial is currently underway through the National Institute of Health (NIH)-sponsored Frequent Hemodialysis Network. The CV effects of NHD will be compared with standard therapy. We speculate that, given our current data, nocturnal hemodialysis will translate into lower CV event rates in ESRD patients.

Additional Reading

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Statins and Proteinuria

by Albert Yeung

Microalbuminuria is a powerful predictor of future cardiovascular (CV) events in diabetic and non-diabetic populations. In the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study, there was a four- to five-fold increase in the risk of CV complications between the highest and lowest decile of urinary albumin excretion rate.¹ The link between microalbuminuria, an early sign of renal dysfunction, and the development of atherosclerotic disease involves a more generalized state of abnormal arteriolar response and endothelial injury, largely influenced by traditional CV risk factors such as hypertension and lipid abnormalities.

Lowering blood pressure (BP) and reducing albuminuria reduces the risk of end-stage renal disease (ESRD) and also that of myocardial infarction (MI), cardiac failure, and stroke. Pharmacologic intervention, especially by blocking the renin-angiotensin system (RAS) with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), has been shown to decrease the progression of micro- to macro-albuminuria and delay the development of chronic renal failure. Even normotensive individuals with albuminuria can benefit from such treatment. Therefore, current guidelines strongly recommend drugs that lower BP and reduce proteinuria.

Clinical Studies of Statins on Renal Function

There is substantial evidence from animal models that hyperlipidemia can cause glomerular injury and accelerate the progression of renal disease. However, human data in this

regard remains sparse. The use of statins has been reported to reduce urinary albumin excretion and even retard progression of diabetic nephropathy. However, the published clinical studies recruited relatively small numbers of patients.

In a randomized, double-blind crossover study, a group of normotensive but hypercholesterolemic type 2 diabetics with microalbuminuria,

by improving tubular function via inhibition of renal endothelin-1 (ET-1) synthesis. ET-1 is strongly chemotactic for monocytes and stimulates both glomerular and interstitial fibroblast proliferation. Blocking ET receptors has been shown to reduce proteinuria.

In a post-hoc subgroup analysis of the Cholesterol and Recurrent Events (CARE) study, pravastatin 40 mg/day reduced the rate of decline in renal

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treated with simvastatin for one year, showed a significant 25% decrease in urinary albumin excretion rate.²

A meta-analysis of 12 studies examined the effects of lipid reduction on the progression of renal disease in a total of 384 patients and found that lipid-lowering drugs could decrease proteinuria in patients with renal disease and preserve glomerular filtration rate.³

In a study of 63 Chinese patients with controlled BP and proteinuria ranging from 300 to 3,000 mg/day, treatment with low-dose pravastatin (10 mg/day) reduced proteinuria by 54%.⁴ Creatinine clearance was unchanged after six months of treatment with pravastatin. The investigators proposed that pravastatin might act

function in subjects having more severe chronic renal impairment, especially those with proteinuria.⁵ On the other hand, treatment with the fibrate, gemfibrozil, was not shown to provide any renoprotective effect in the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT). In a prospective, controlled open-label study, atorvastatin reduced proteinuria and the rate of progression of renal disease. The benefits appeared to be additive to that obtained from treatment with ACE inhibitors and ARBs.⁶

These clinical observations lend support to the findings in experimental Heymann nephritis in rats with severe nephropathy that a combination of simvastatin and lisinopril



afforded considerable protection against the emergence of glomerulosclerosis, tubular damage and interstitial inflammation, while either drug alone had little effect.

Effects of Rosuvastatin on Renal Function

In the June 26, 2004 issue of *The Lancet*, Wolfe drew attention to data submitted to the American FDA showing an increased frequency of

Patients with chronic renal disease often have elevated low-density lipoprotein cholesterol (LDL-C), low high-density lipoprotein cholesterol (HDL-C) and small, dense LDL particles that can directly damage the glomeruli through the formation of oxidized LDL-C.

persistent proteinuria and microscopic hematuria in a small percentage of patients exposed primarily to high-dose (> 40 mg/day) rosuvastatin. The occurrence of proteinuria and hematuria was dose-related, with 1.3% of patients treated with 40 mg/day being affected.

In rebuttal, on behalf of the manufacturer of rosuvastatin, Vidt et al published a retrospective analysis of in-house data on the renal function of a diverse group of over 10,000 trial patients who had received rosuvastatin, some for up to 3.8 years.⁷ There was a small, dose-related increase in the frequency of proteinuria in patients treated with rosuvastatin.

Microscopic hematuria was recorded in 1.2% to 1.8% of patients taking rosuvastatin, 1.1% to 1.8% taking atorvastatin, 1.0% to 2.8% taking simvastatin and 0.9% taking placebo. However, contrary to the charge that rosuvastatin might cause renal damage, glomerular filtration rate was found to be unchanged or slightly

improved after rosuvastatin therapy, across all doses, irrespective of whether the subjects had detectable proteinuria before or during the period of statin treatment. No case of acute renal failure or persistent renal damage was mentioned in the report.

Mechanism of Action of Statins

Patients with chronic renal disease often have elevated low-density lipoprotein cholesterol (LDL-C), low

high-density lipoprotein cholesterol (HDL-C) and small, dense LDL particles that can directly damage the glomeruli through the formation of oxidized LDL-C. Aside from lowering the concentration of LDL-C, statins may confer renoprotection by pleiotropic (non-cholesterol dependent) effects such as reducing oxidative stress and inflammation, improving endothelial function, inhibiting thrombogenic response in the vascular wall, suppressing the proliferative response of mesangial and vascular smooth muscle cells, and immune-modulation.

In the proximal tubule of the nephron, protein is reabsorbed by receptor-mediated endocytosis (RME), a process requiring prenylated GTP-binding proteins. RME can be impaired by statins and in vitro studies have shown that several statins can strongly inhibit protein uptake by human proximal tubular kidney cells in a concentration-dependent manner. Electrophoresis of urine samples from patients treated

with rosuvastatin show a tubular (rather than glomerular) pattern of excretion, with increased levels of β -1 microglobulin and retinol binding protein, both of which undergo RME. The extent of drug clearance by the renal route and the high potency of rosuvastatin might explain the increased frequency of proteinuria observed with this agent when compared to the other marketed statins. It has therefore been hypothesized that statins could, under certain circumstances, cause tubular proteinuria while being renoprotective. This will need to be substantiated in clinical studies. Furthermore, the issue of whether microscopic hematuria is a complication of rosuvastatin or of statin therapy in general also remains an open question.

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Do Coffee, Chocolate or Cocoa Affect Blood Pressure?

by Carl Abbott

The 2005 CHEP Recommendations for the Management of Hypertension list prescription drugs and “other substances” that can induce or aggravate hypertension. The current list of other substances includes licorice root, sea salts, stimulants including cocaine, table salt and excessive alcohol.

Lifestyle changes, involving limits to the use of these substances, are often recommended as an essential element for prevention in normotensive patients at increased risk of hypertension and for management strategies in established hypertension. Low-risk alcohol consumption is recommended, but no limits have been recommended for coffee, said to be the most abundantly consumed stimulant, or for other popular drinks and foods such as cocoa and chocolate.

Many of our hospitals now offer coffee outlets, catering to patients and staff. They are very popular. Long queues are a common sight for both the regular and decaffeinated offerings. Conflicting evidence exists for the effects of coffee on blood pressure (BP). Restriction is recommended for benign cardiac ectopy. The assumption is that caffeine is the sympathetic nervous system stimulant in coffee.

Robert Corti et al¹ examined the BP (measured with a Dynamap) and muscle sympathetic activity (MSA, via a peroneal nerve) responses to drinking a triple espresso, a triple decaffeinated espresso, an equivalent (250 mg) amount of IV caffeine and IV saline placebo in six habitual and nine non-habitual normotensive (mean BP 126/69 mmHg)

coffee drinkers. Regular and decaffeinated coffee as well as IV caffeine acutely induced similar increases in MSA and BP in the non-habituated group. An increase in MSA without a change in BP was seen in the habituated group.

The authors concluded that some substance(s) other than caffeine stimulates MSA and increases BP; coffee restrictions may not be necessary for habitual coffee drinkers; and normotensive patients without a genetic predisposition for hypertension may drink coffee without risk. The chronic effects of coffee in subjects with or without hypertension still needs to be explored.

Coffee drinkers may also enjoy chocolate. The plant polyphenols, especially high in dark chocolate, can lower

not with the white PF bars. After 14 days, target BP was not reached. BMI, electrolyte and glucose measures were unchanged. The mechanism is unclear, but if your patients love chocolate and have systolic hypertension, the dark varieties can be recommended though adjunct therapy will likely be needed. Lipids should be monitored unless they are known to be unequivocally normal.

In the same journal,³ a double-blind cross-over study of the effects of a subclass of flavonoids of cocoa beans on the pool of nitric oxide (NO) and on endothelial-dependent dilation were compared in 20 participants, each with a minimum of one CV risk factor (*e.g.*, smoking, diabetes mellitus, hypertension). Following a single

... coffee restrictions may not be necessary for habitual coffee drinkers, and normotensive patients without a genetic predisposition for hypertension may drink coffee without risk. The chronic effects of coffee in subjects with or without hypertension still needs to be explored.

BP in animals, but is it good for human hypertension? Four German investigators² conducted a randomized crossover study in six men and seven women, aged 55 to 64 years with normal BMIs and recently diagnosed but untreated systolic hypertension (mean BP 154/84 mmHg), using 100 g caloric-balanced (480 kcal) dark, polyphenol rich (PR) chocolate bars or 100 g white, polyphenol-free (PF) bars for 14 days. Seated BP (Omron HEM 722) was measured daily. BP fell significantly within 10 days with the dark PR chocolate but

ingestion of 100 ml of cocoa, either rich (176 mg) or low (< 10 mg) in flavan-3-ols, only the rich form of cocoa increased NO concentrations and improved endothelial function. Both the mechanism and the long-term effects are unknown, and the cocoa brands must be carefully chosen.

Unfortunately, polyphenols with reputed anti-oxidant properties on circulation can be destroyed during the fermentation of cocoa and the ensuing heating process used in the production of chocolate. A Swiss company has



Perioperative Beta-blockers

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with a major cardiac event, compared to 30 of the 250 patients taking placebo ($p = 0.4$). A larger number of subjects treated with metoprolol also presented with bradycardia or hypotension requiring treatment, which is not surprising.

The Diabetic Postoperative Mortality and Morbidity (DIPOM) study, presented at the Congress of the American Heart Association in the fall of 2004, also evaluated the impact of metoprolol in 921 diabetic patients undergoing noncardiac surgery. After 18 months of follow-up, 21% of patients in the metoprolol group presented with a major cardiac event, compared to 20% in the placebo group ($p = 0.53$).

We must await final publication of these studies before conducting a complete analysis. Still, it seems that the results from these two studies, along with those from eight other small studies that reported negative findings with beta-blockers (with a total of approximately 1,500 patients), triggers some debate concerning the efficacy of perioperative beta-blockers.

More Answers to Come

The final response to this question may come from the Perioperative Ischemic Evaluation (POISE) study, which is

underway. This international multicenter study, funded by the Canadian Institutes of Health Research (CIHR), is evaluating the efficacy of metoprolol in preventing major perioperative cardiovascular events. To date, more

in patients with evidence of preoperative ischemia is probably justifiable. Beta-blockers should not be used if the perioperative cardiac risk is low because iatrogenic complications may ensue. They should not be combined

... there is some evidence that can justify the use of perioperative beta-blockers to reduce the incidence of cardiac complications, but this evidence is far from reliable. The evaluation of the risk/benefit ratio should be done individually for each patient. Beta-blockers should be used for patients with clear indications for this class of medication (post-infarction, cardiac failure).

than 3,500 subjects have been enrolled in this study, which has a total recruitment objective of 10,000 patients. The results should be available before 2007.

In the meantime, what should we do? As we have seen, there is some evidence that can justify the use of perioperative beta-blockers to reduce the incidence of cardiac complications, but this evidence is far from reliable. Evaluation of the risk/benefit ratio should be done individually for each patient. Beta-blockers should be used for patients with clear indications for this class of medication (post-infarction, cardiac failure). The use of beta-blockers

with a non-dihydropyridine calcium channel blocker because of the risk of heart block. There are still many questions that must be answered clearly, and the importance of these questions increases with the growing number of surgeries in increasingly older patients.

Recommended reading:

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Coffee, chocolate, cocoa

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recently patented a process to remove the polyphenols before processing with the intention of re-inserting them later, with the hope their product will have

additional benefits from higher concentrations. Massive advertising is sure to come soon!

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