In the name of GOD

Hypertension Management Before Surgery In CKD

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 Preoperative evaluation and preparation of CRF patients is mandatory to minimize perioperative morbidity and mortality.

•Preexisting hypertension is the most common medical reason for postponing surgery

- Hypertension is found in more than 80% of CRF patients.
- Whether hypertension is a cause or a result of CRF remains debatable



- The most common cause of hypertension is volume overload
- Nonvolume-dependent hypertension is related to an altered autonomichormonal milieu of uremia.



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Factor	Dominant Mechanism
Impaired sodium excretion	Expansion of ECF volume
Activation of RAS	Direct vasoconstriction Sympathetic activation
Sympathetic activation	Direct vasoconstriction Stimulation of renin release
Imbalance in prostaglandins or kinins	Vasoconstriction
Endothelin	Direct vasoconstriction Renal injury
Reduced nitric oxide	Loss of vasodilator effect



Common causes of acute intraoperative increases in BP

- sympathetic stimulation during laryngoscopy and endotracheal intubation
- surgical stimulation (Inadequate anesthetic depth during painful surgical stimulation)
- emergence and tracheal extubation
- hypercarbia or hypoxemia (due to sympathetic stimulation) -higher fraction of inspired oxygen (FiO2)
- Hypervolemia
- withdrawal of antihypertensive medications
- bladder distention



Seminars in Dialysis

Perioperative Management of the Hemodialysis Patient

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Hypertension is common in HD patients, and good control should be achieved to minimize perioperative instability.

Management will include achieving the correct dry weight with optimization of fluid removal, adjusting the dose of antihypertensive drugs, or adding additional agents.



The preanesthesia consultation involves:

- • overall risk assessment
- blood pressure measurement
- determination of **target BP** values for the intraoperative period
- decisions regarding whether to employ <u>noninvasive BP monitoring</u> or an <u>intra-arterial catheter for direct continuous monitoring</u>

When assessing patients for anaesthesia who have elevated blood pressure, a number of questions must be answered.

Is the patient known to be hypertensive on a previous occasion?

Are they on antihypertensive medication?

Does the patient have a treatable cause for their hypertension?

Does the blood pressure control need alteration before surgery?

Does the patient have "white coat" hypertension?





- In the absence of a recent ambulatory arterial pressure measurement, experts propose that a office baseline measure should be obtained (ideally within 30 days) before the day of surgery to limit the effects of white coat hypertension
- These preoperative measures may be used for setting intraoperative arterial pressure targets.



In patients more than 65 yr of age undergoing non-cardiac surgery, there is evidence that low preoperative arterial pressure is more strongly associated with increased postoperative risk of mortality than high pressure using primary care data.

In a large study, increased mortality risk was identified in patients with a preoperative systolic arterial pressure <119 mm Hg, diastolic <63 mm Hg, and pulse pressure <37 mm Hg.



Perioperative Quality Initiative consensus statement on preoperative blood pressure, risk and outcomes for elective surgery

> Examples of the association of preoperative arterial pressure and postoperative mortality. The unadjusted data on the left demonstrate the Jcurve phenomenon for the association between preoperative systolic, diastolic, and pulse pressures, and postoperative mortality.

> > Br J Anaesth 2017





European Heart Journal (2018) **39**, 3021–3104 / doi:10.1093/eurheartj/ehy339

2018 ESC/ESH Guidelines for the management of arterial hypertension

 While a BP elevation is per se not a strong risk factor for CV complications in noncardiac surgery, overall CV risk assessment, including the search for HMOD hypertension mediated organ damage, is important in treated and untreated hypertensive patients, and mandatory when a BP elevation is newly detected

> The effect of chronic hypertension on <u>perioperative risk</u> is determined primarily by the presence of <u>target organ damage</u>, that is, coronary artery disease, stroke, heart failure, and renal failure, all of which are known to affect <u>perioperative morbidity and mortality</u>.

There are **no** randomized clinical trial data showing what the optimal blood pressure should be at the time of surgery.



The patients with preoperative isolated systolic hypertension(where the pressure is greater than <u>180 mmHg</u> or the pulse pressure is greater than <u>80 mmHg</u>) had a 40% increase in perioperative cardiovascular events. Patients with untreated or poorly controlled hypertension have increased intraoperative hemodynamic instability and an increased risk in the presence of a pre- operative diastolic blood pressure >110 mm Hg

Increased complications including myocardial infarction, myocardial ischemia, dysrhythmias, cerebrovascular events, and renal failure have been reported if the preoperative diastolic blood pressure is <u>110 mmHg</u> or higher.





- Evidence-Based Guideline for the management of high BP in adults, suggests a BP goal of < 140/90 mmHg in patients with CKD.
- However, this recommendation and goal are for long-term management.
- Although, a specific guideline for an <u>upper acceptable limit of</u> <u>preoperative BP in CKD patient</u> is not available, yet, a patient can be accepted for elective surgery if the preoperative BP is < 180/105 mmHg





ESC/ESH GUIDELINES

2018 ESC/ESH Guidelines for the management of arterial hypertension



 Postponing necessary surgery is usually not warranted in patients with grade 1 or 2 hypertension, whereas in those with an SBP >_180 mmHg and/or DBP >_110 mmHg, deferring the intervention until BP is reduced or controlled is advisable, except for emergency situations



 For most patients with chronic hypertension, experts suggest maintaining BP within 20 percent of resting baseline value and mean arterial pressure (MAP) >65 mmHg (Grade 2C).

• Some patients may require a higher MAP.

 Lability of perioperative BP is likely, and we prevent and treat both hypertension and hypotension



A mean arterial pressure of 65 mmHg may be suboptimal and *predispose the patient to*

AKI in chronic hypertensive patients.

•

As intraoperative hypotension adversely affects the *renal microvasculature* and has been shown to be associated *with increased 30-day operative mortality in non-cardiac surgery*

maintenance of BP within 20% of baseline can be regarded as paramount especially for those who are at risk of developing AKI.





What seems to be also important is to **avoid** large perioperative BP fluctuations.

These patients often have higher BP and their auto regulations are also set at higher levels

It will be prudent to reduce the blood pressure (if presented with high BP, e.g. 180/100) by 20% during the intraoperative period, and then slowly targeting towards the goal in the postoperative period over the next few days







<u>JAMA</u>. 2017 Oct 10; 318(14): 1346–1357. Published online 2017 Oct 10. Prepublished online 2017 Sep 27. doi: <u>10.1001/jama.2017.14172</u> PMCID: PMC5710560 PMID: <u>28973220</u>

Effect of Individualized vs Standard Blood Pressure Management Strategies on Postoperative Organ Dysfunction Among High-Risk Patients Undergoing Major Surgery A Randomized Clinical Trial



Among patients predominantly undergoing abdominal surgery who were at increased postoperative risk, management targeting an individualized systolic blood pressure, compared with standard management, reduced the risk of <u>postoperative organ dysfunction</u>.



Figure 3.

Kaplan-Meier Estimates of the Probability of Postoperative Organ Dysfunction by Day 30 After Surgery

- There is no clear evidence in favour or against one vs another antihypertensive treatment mode in patients undergoing <u>non-cardiac</u> <u>surgery</u>, and thus the general drug treatment algorithms apply to these patients as well.
- However, the perioperative use of beta- blockers has been the object of controversy for many years, and the concern has recently been revived by meta-analyses showing some increase in the risk of hypotension, stroke, and mortality in patients on perioperative betablockers vs placebo

Continuation of beta-blockers is nevertheless recommended in hypertensive patients on chronic beta-blocker treatment in whom their <u>abrupt discontinuation</u> <u>may lead to BP or heart rate rebounds</u>



oral antihypertensive medications should be continued up to the time of surgery



If the patient failed to take a morning dose of an antihypertensive medication, the missed dose is administered with a sip of water in the preoperative area when feasible



What about RAS Blockers

 Many centers routinely withhold angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) for 24 hours before surgery or administer the evening dose before elective surgery (but not on the morning of surgery), particularly if significant perioperative fluid shifts are anticipated.



The Cochrane Database of Systematic Reviews

Cochrane Library Cochrane Database of Systematic Reviews

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Cochrane Database Syst Rev. 2016 Jan;

Perioperative angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers for preventing mortality and morbidity in adults

Perioperative angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers for preventing mortality and morbidity in adults (Review)

Zou Z, Yuan HB, Yang B, Xu F, Chen XY, Liu GJ, Shi XY

Authors' conclusions Overall, this review did not find evidence to support that perioperative ACEIs or ARBs can prevent mortality, morbidity, and complications (hypotension, perioperative cerebrovascular complications, and cardiac surgery-related renal failure).

We found no evidence showing that the use of these drugs may reduce the rate of **acute myocardial infarction.**

However, ACEIs or ARBs may increase cardiac output perioperatively



PERIOPERATIVE MEDICINE

Withholding *versus* Continuing Angiotensin-converting Enzyme Inhibitors or Angiotensin II Receptor Blockers before Noncardiac Surgery

An Analysis of the Vascular events In noncardiac Surgery patlents cOhort evaluatioN Prospective Cohort

- Conclusions
- This international prospective cohort study suggests that withholding ACEI/ARBs on the day of a noncardiac surgery may reduce the risk of perioperative death, stroke, or myocardial injury in patients who take these medications chronically.

A	Medication withheld	Outcome	Events in withheld vs. continued	aRR (95% Cl), p-value	
	ACEI/ARBs	Death, MINS, or stroke Death MINS Stroke Intraop. hypotension Postop. hypotension MI (Exploratory) Death, MI, or stroke (Exploratory)	150/1245 (12.0%) vs. 459/3557 (12.9%) 25/1245 (2.0%) vs. 74/3557 (2.1%) 132/1245 (10.6%) vs. 399/3541 (11.3%) 8/1245 (0.6%) vs. 26/3557 (0.7%) 290/1245 (23.3%) vs. 1017/3557 (28.6%) 242/1245 (19.4%) vs. 719/3557 (20.2%) 57/1245 (4.6%) vs. 148/3557 (4.2%) 78/1245 (6.3%) vs. 221/3557 (6.2%)	0.82 (0.70-0.96), 0.01 0.69 (0.39-1.24), 0.21 ← 0.84 (0.70-0.998), 0.048 0.81 (0.30-2.2), 0.68 ← 0.80 (0.73-0.88), <0.001 0.92 (0.77-1.10), 0.36 0.91 (0.66-1.27), 0.59 0.81 (0.62-1.03), 0.08	
В	Hypotension	Outcome	Events in exposed vs. unexposed	aRR (95% CI), p-value	
	Intraoperative	Death, MINS, or stroke Death MINS Stroke Postop. hypotension MI (Exploratory) Death, MI, or stroke (Exploratory)	464/4162 (11.1%) vs. 945/10525 (9.0%) 133/4162 (3.2%) vs. 169/10525 (1.6%) 353/4138 (8.5%) vs. 807/10496 (7.7%) 32/4162 (0.8%) vs. 58/10525 (0.6%) 1133/4162 (27.2%) vs. 1595/10525 (15.2%) 137/4162 (3.3%) vs. 309/10525 (2.9%) 273/4162 (6.6%) vs. 472/10525 (4.5%)	1.11 (0.98-1.25), 0.09 1.41 (1.07-1.86), 0.02 1.04 (0.90-1.20), 0.58 1.14 (0.85-1.54), 0.37 1.65 (1.48-1.84), <0.001 1.05 (0.80-1.35), 0.74 1.23 (1.03-1.47), 0.03	
	Postoperative	Death, MINS, or stroke Death MINS Stroke MI (Exploratory) Death, MI, or stroke (Exploratory)	439/2728 (16.1%) vs. 970/11959 (8.1%) 125/2728 (4.6%) vs. 177/11959 (1.5%) 346/2703 (12.8%) vs. 814/11931 (6.8%) 24/2728 (0.9%) vs. 66/11959 (0.6%) 153/2728 (5.6%) vs. 293/11959 (2.5%) 266/2728 (9.8%) vs. 479/11959 (4.0%)	1.68 (1.53–1.85), <0.001 2.20 (1.90–2.54), <0.001 1.63 (1.44–1.84), <0.001 1.73 (0.67–4.51), 0.26 1.96 (1.66–2.32), <0.001 2.01 (1.72–2.33), <0.001	* * *
				0.50	0.75 1.00 1.50 2.00 3.00 Adjusted Relative Risk
Fig. hibi	2. (A) Adjusted ors or angioter	association between wit sin II receptor blockers	hholding <i>versus</i> continuing preo (ARBs) with postoperative 30-d	perative angiotensin ay death from any c	-converting enzyme (ACE) in- cause, myocardial injury after

Vision study



Fig. 3. Clinically significant hypotension in the postoperative period. In total, 2,860 of 14,687 patients (19.5%) experienced at least one episode of clinically significant hypotension after their surgery; 2,728 (95.4%) of those patients experienced a hypotensive episode by postoperative day (POD) 3. OR = operating room; PACU = postanesthesia care unit.

day

"...findings suggest that administration [of angiotensinconverting enzyme inhibitors or angiotensin II receptor blockers] on the day of surgery is hazardous..."

A Systematic Review of Outcomes Associated With Withholding or Continuing Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers Before Noncardiac Surgery



2018 International Anesthesia Research Society



Mortality associated with withholding or continuing ACE-I or ARB therapy



Intraoperative hypotension associated with withholding or continuing ACE-I or ARB therapy.



Major adverse cardiac events associated with withholding or continuing ACE-I or ARB therapy

Intra-operatively the neurohumoral response to surgery causes a sympathetic response, releasing vasopressin, aldosterone and cortisol in the "fight or flight" response. One of the aims of this is to aid salt and water retention protecting the renal vasculature. ** N.B. Anaesthetic agents, ACE inhibitors and NSAIDs will alter this protective response





Original Investigation

Acute Kidney Injury and Death Associated With Renin Angiotensin System Blockade in Cardiothoracic Surgery: A Meta-analysis of Observational Studies

Rabi Yacoub, MD,¹ Nilang Patel, MD,^{2,3} James W. Lohr, MD,^{4,5} Srini Rajagopalan, PhD,⁶ Nader Nader, MD, PhD,⁷ and Pradeep Arora, MD^{4,5}

Background: Acute kidney injury (AKI) is a common complication after cardiovascular surgery. The use of **RAS Blocker** renin angiotensin system (RAS) blockers preoperatively is controversial due to conflicting results of their effect **RAS Blocker** use use and and Study Postoperative Events ID OR (95% CI) OR (95% CI) Weigh **Mortality** Full Article **AKI** 1.42 (1.26, 1.60) Argalious et a 822/60 2.76 1.06 (0.52, 2.15) 18/225 15/197 Arora et al 1.58 (1.27, 1.97) 321/707 1.37 (0.70, 2.66) 22/707 15/653 3.14 Bandeali et a 1.34 (1.18, 1.53) 522/3983 0.20 (0.05, 0.89) 17/224 Barodka et al. 2/122 0.89 (0.71, 1.10) 144/3983 199/4906 16.33 Benedetto et a 0.66 (0.49, 0.89) 160/440 135/291 5.42 Cittanova et al 1.99 (1.05, 3.79) 20/57 41/192 3.01 Barodka et a 1.45 (0.53, 4.01) 7/122 9/224 1.43 4.83 2.28 (1.57, 3.31) 43/1765 Drenger et al. 84/1562 Benedetto et al 0.80 (0.30, 2.11) 8/281 9/255 1.56 Karkouti et al 0.89 (0.76, 1.04) 462/2003 367/1457 6 47 Kincaid et al 3.17 (1.60, 6.24) 30/545 12/664 2.83 Drenger et al 1.16 (0.72, 1.86) 35/1562 35/1800 5.67 Metz et al. 1.39 (1.14, 1.70) 233/1080 244/1476 6.19 Miceli et al. 1.92 (1.13, 3.26) 40/3052 21/3052 4.68 Miceli et al 1.32 (1.07, 1.63) 217/3052 167/3052 6.13 Ouzounian et a 0.80 (0.66, 0.98) 201/2684 6.17 Ouzounian et a 1.14 (0.85, 1.54) 108/3262 78/2684 11.47 199/3262 Provenchere et a 0.84 (0.54, 1.30) 33/212 79/437 4.29 Pretorius et a 1.29 (0.10, 16.04) 2/19 1/12 0.24 Radaelli et a 1.26 (0.98, 1.61) 161/163 120/1504 5.84 Radaelli et a 1.45 (1.16, 1.81) 213/1635 141/1504 15.83 Rader et al 243/3437 6.30 1.00 (0.84, 1.21) 244/3437 Rady et al. 1.37 (1.08, 1.73) 104/3025 211/8305 5.91 Rader et al 0.92 (0.62, 1.37) 47/3437 51/3437 7.46 Yoo et al 1.07 (0.67, 1.70) 62/296 35/176 4.14 Rady et al 1.37 (1.11, 1.70) 133/302 269/8305 16.84 Pretorius et al. 2 0.12 (0.01, 0.94) 1/151 8/147 0.47 1.20 (1.04, 1.39) Subtotal (I-squared = 83.4%, p = 0.000) 3677/31585 3107/35993 88.22 Salem et a 1.40 (0.92, 2.12) 36/884 63/2140 6.96 1.17 (0.64, 2.12) 37/1161 3.81 Weightman 16/432 Abstract Chughtai et a 2.40 (1.42, 4.08) 80/209 24/117 3.70 Yoo et al. 0.29 (0.03, 3.28) 1/206 2/176 0.26 Neill et a 1.64 (0.51, 5.22) 13/142 4/69 1.32 Huang et al. 0.71 (0.22, 2.26) 1.10 5/20/ 7/208 Ho et al. 0.38 (0.15, 0.93) 9/134 13/81 1.95 Huang et al 0.38 (0.19, 0.79) 11/298 27/298 2.63 Pretorius et al 3 1 47 (0 24 8 92) 3/151 2/147 0.46 1.11 (0.48, 2.54) 21/59 14/42 2.17 Tantisattamo et al Webb et al. (Excluded) 0/47 0/49 0.00 Subtotal (I-squared = 82.2%, p = 0.000) 0.92 (0.40, 2.11) 134/842 82/607 11.78 Overall (I-squared = 20.5%, p = 0.215) 1.20 (1.06, 1.35) 838/23418 954/31000 100.00 Overall (I-squared = 82.5%, p = 0.000) 1.17 (1.01, 1.36) 3811/32427 100.00 NOTE: Weights are from random effects analys NOTE: Weights are from random effects analysi Publication bias coefficient = -0.75, SD = 0.9, p = 0.4, 95% CI = -2.62 to 1.13 Publication bias coefficient = -0.22, SD = 0.49, p = 0.6, 95% CI = -1.28 to 0.83

Figure 3. Renin angiotensin system blocker use and mortality: forest plot and analysis results. Abbreviations: CI, confidence interval; OR, odds ratio; p, probability value SD, standard deviation.

Figure 2. Renin angiotensin system blocker use and postoperative acute kidney injury: forest plot and analysis results. Abbrevia tions: CI. confidence interval: OR. odds ratio: p. probabilitv value SD. standard deviation.

Cardiothorasic

surgery



RESEARCH ARTICLE

Pre- and/or Intra-Operative Prescription of Diuretics, but Not Renin-Angiotensin-System Inhibitors, Is Significantly Associated with Acute Kidney Injury after Non-Cardiac Surgery: A Retrospective Cohort Study

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1 Department of Nephrology, Kyoto Katsura Hospital, 17 Yamada-hirao-cho, Nishikyo-ku, Kyoto, 6158256, Japan, 2 First Department of Internal Medicine, Nara Medical University, 840 Shilo-cho, Kashihara-shi, Nara, Conclusions Prescription of diuretics, but not ACE-I/ARB, was independently associated with **POStoperative AKI** after non-cardiac surgery, especially in patients with low propensity for diuretic use. It might be reasonable to withhold preoperative diuretics in these patients.



ORIGINAL RESEARCH ARTICLE

Association Between Preoperative Diuretic Use and In-hospital Outcomes After Cardiac Surgery

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Conclusion:

Preoperative diuretics use is associated with an increased incidence of MAEs after cardiac surgery.

In patients in whom diuretics could be safely withheld (patients on diuretics for <u>hypertension</u> and <u>peripheral edema</u> and <u>patients with mild systolic dysfunction</u> and <u>compensated</u> <u>heart failure</u>), an attempt can be made to stop it prior to cardiac surgery. Given our results, it might be prudent to more carefully examine the need for preoperative diuretic use in patients undergoing cardiac surgery. **Table 2** Incidence of major adverse events and individual secondary outcomes in the "All cardiac surgery group"

	Preoperative diuretic		
Dutcome	Yes (n = 3546)	No (n = 9047)	P ^a -value
Najor adverse events, n (%)	1748 (49.29)	3212 (35.50)	<0.0001
n-hospital mortality, n (%)	269 (7.59)	347 (3.84)	<0.0001
Postoperative renal dysfunction, n (%)	716 (20.19)	880 (9.73)	< 0.0001
ostoperative stroke, n (%)	125 (3.53)	259 (2.86)	0.06
Postoperative atrial fibrillation, n (%)	1238 (34.91)	2388 (26.40)	<0.0001
Postoperative myocardial infarction, n (%)	115 (3.24)	239 (2.64)	0.07

BJA

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Perioperative Quality Initiative consensus statement on preoperative blood pressure, risk and outcomes for elective surgery



Thiazide diuretic / Calcium channel blocker No evidence to stop

> Loop diuretics Consider per patient

β Blocker Continue when prescribed for congestive heart failure or myocardial infarction

Do not start preoperatively for risk reduction

No evidence to lower high blood pressure immediately preoperatively

> Preoperative blood pressure values may be used to define perioperative blood pressure targets

Preoperative hypotension may be associated with increased risk

Calcium channel blockers — Patients

receiving calcium channel blockers may have an increased incidence of postoperative bleeding, probably due to inhibition of platelet aggregation .

The multiple benefits of these drugs probably outweigh the small risk of continued therapy.



Induction

Fenoldopam

a peripheral dopamine-1-receptor agonist, induces peripheral vasodilation; administered by intravenous infusion used as an antihypertensive agent postoperatively and also IV to treat ahypertensive crises



Only agent that improve renal perfusion

Concomitant use of fenoldopam with a beta-blocker should be avoided if possible, as unexpected hypotension can result from beta-blocker inhibition of sympathetic-mediated reflex tachycardia in response to fenoldopam



2018 ESC/ESH Guidelines for the management of arterial hypertension

erioperative management of hypertension		
Recommendations	Class ^a	Level
It is recommended that newly diagnosed hypertensive patients who are scheduled for elective surgery should be preoperatively screened for HMOD and CV risk.	I	с
It is recommended to avoid large perioperative BP fluctuations during the perioperative period. ⁵⁸⁷	I.	С
Non-cardiac surgery may not be deferred in patients with grade 1 or 2 hypertension (SBP <180 mmHg; DBP <110 mmHg).	ПР	С
Perioperative continuation of beta-blockers is recommended in hypertensive patients on chronic treatment with these drugs. ^{592,593}	I	в
Abrupt discontinuation of beta-blockers or centrally acting agents (e.g. clonidine) is potentially harmful and is not recommended. ^{589,594}	ш	В
Transient preoperative discontinuation of RAS blockers should be considered in patients with hypertension undergoing non- cardiac surgery.	lla	с

BP = blood pressure; CV = cardiovascular; DBP = diastolic blood pressure; HMOD = hypertension-mediated organ damage; RAS = renin-angiotensin system; SBP = systolic blood pressure.

^aClass of recommendation.

^bLevel of evidence.



Preoperative	Intraoperative	Postoperative
SAP ≤ 180 mmHg, DAP≤110 mmHg	MAP not lower than 25–30% of awake	Resume antihypertensive drugs upon oral intake or substitute i.v.
ECG, serum creatinine, electrolytes (diuretics) search for target organ damage (heart, brain, kidney)	Attenuate sympathetic response to laryngoscopy (or use laryngeal mask)	Measure blood pressure every 5–15 min first hour then every 30 min until 3 h postoperative
Antihypertensive drugs; continue day of surgery: b-blockers, CCB; stop day of surgery: diuretics, ACEI, ARB	Consider use of noninvasive cardiac output monitoring and near-infrared spectroscopy (NIRS)	Treat postoperative hypertension to MAP > 100 and <130 mmHg and HR 50 bpm; <u>Metoprolol</u> : repeat 2–5 mg bolus i.v.; <u>labetolol</u> : repeat 10–20 mg bolus i.v.; <u>nicardipine</u> : 0.5–1 ug/kg/min i.v.; <u>nitroglycerine:</u> 0.1–5 ug/kg/min i.v.

((د)



