Prostaglandin E_1 attenuates the hypertensive response to tracheal extubation

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Purpose: *Tracheal extubation causes hypertension and tachycardia, which may cause imbalance between myocardial oxygen demand and supply in patients at risk of coronary artery disease. We conducted a randomized, controlled study to evaluate the effects of 0.05 or 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ prostaglandin E_1 (PGE_1) iv on haemodynamic variables occurring during tracheal extubation and emergence from anaesthesia and compared them in patients receiving either lidocaine or saline.*

Methods: *Eighty ASA physical status I patients undergoing elective surgery were enrolled in the current study. Anaesthesia was maintained with sevoflurane 1.0%–2.5% (ET concentration) and nitrous oxide 60% in oxygen. Muscle relaxation was achieved with vecuronium. The patients were randomly assigned to receive one of four treatments (n = 20 each): saline (control), 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ PGE_1, 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ PGE_1, or 1 $mg \cdot kg^{-1}$ lidocaine. PGE_1 was infused from completion of surgery until five minutes after tracheal extubation. Changes in heart rate (HR) and blood pressure (BP) were measured during and after tracheal extubation.*

Results: *In the control group, the HR, systolic BP, and diastolic BP increased during tracheal extubation. Administration of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ PGE_1 and 1 $mg \cdot kg^{-1}$ lidocaine attenuated the increases in BP although 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ PGE_1 failed to do so. The inhibitory effect of the 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ PGE_1 on BP was similar to that of lidocaine 1 $mg \cdot kg^{-1}$ iv. The increase in HR was attenuated by lidocaine but not by PGE_1.*

Conclusion: *The intravenous infusion of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ PGE_1 given during emergence from anaesthesia and tracheal extubation is a useful method for attenuating the hypertension associated with noxious stimuli during this period.*

Objectif: *L'intubation trachéale provoque de l'hypertension et de la tachycardie, sources de déséquilibre entre la demande et l'apport en oxygène chez les sujets à risque d'ischémie myocardique. Les auteurs ont mené une étude aléatoire contrôlée dans le but d'évaluer les effets de 0,05 ou 0,1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ de prostaglandine E_1 (PGE_1) iv sur les variables hémodynamiques mesurées à l'extubation et pendant le réveil postanesthésique et les comparer chez les patients recevant soit de la lidocaïne soit du sol. physiologique.*

Méthodes: *L'étude présente incluait 84 patients ASA I programmés pour une chirurgie non urgente. L'anesthésie était maintenue avec du sévoflurane 1,0–2,5% (concentration téléexpiratoire) et du protoxyde d'azote 60% en oxygène. La curarisation était assurée par du vécuronium. Les patients étaient répartis pour recevoir une des quatre alternatives suivantes: sol. physiologique (contrôle), PGE_1 0,05 $\mu g \cdot kg^{-1} \cdot min^{-1}$, PGE^1 0,1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ ou lidocaïne 1 $mg \cdot kg^{-1}$. La perfusion de PGE_1 était commencée à la fin de la chirurgie et arrêtée cinq minutes après l'extubation. Les changements de la fréquence cardiaque (Fc) et de la pression artérielle (PA) étaient mesurés avant et après l'extubation.*

Résultats: *Dans le groupe contrôle, la Fc et la PA systolique et diastolique ont augmenté à l'extubation. L'administration de PGE_1 0,1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ et de lidocaïne 1 $mg \cdot kg^{-1}$ ont atténué l'augmentation de PA alors que la PGE_1 0,005 $\mu g \cdot kg^{-1} \cdot min^{-1}$ n'a pas eu cet effet. L'effet inhibiteur de PGE_1 0,1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ sur la PA était identique à celui de la lidocaïne 1 $mg \cdot kg^{-1}$. L'augmentation de Fc a été atténuée par la lidocaïne mais pas par la PGE_1.*

Conclusion: *Une perfusion intraveineuse de PGE1 0,1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, administrée au moment du réveil postanesthésique et de l'extubation, constitue une méthode valable pour atténuer l'hypertension associée aux stimuli nociceptifs de cette période.*

Key words

ANAESTHETIC TECHNIQUES: extubation;
COMPLICATIONS: hypertension, tachycardia;
PHARMACOLOGY: prostaglandin E_1.

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Accepted for publication on 21 March, 1996.

Tracheal intubation often provokes cardiovascular changes with marked increases in blood pressure (BP) and heart rate (HR).[1–3] Tracheal extubation also causes

TABLE I Timing of administration of prostaglandin E_1 (PGE_1), lidocaine, and saline in the four groups (double dummy technique).

	Infusion	*Injection*
	From the end of surgery until 5 min after tracheal extubation	*3 min after completion of surgery (2 min before tracheal extubation)*
Control group	Saline	Saline
Lidocaine group	Saline	Lidocaine 1 $mg \cdot kg^{-1}$
PGE_1 0.05 group	PGE_1 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$	Saline
PGE_1 0.1 group	PGE_1 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	Saline

All injections were prepared in a 5 ml volume. All infusions were prepared in a 50 ml syringe.

hypertension and tachycardia.[4] These haemodynamic changes during extubation and emergence from anaesthesia may cause angina pectoris or acute myocardial infarction in patients with coronary arterial disease (CAD) and in those with risk factors for CAD.[4,5] A variety of drugs has been recommended for the control of these haemodynamic events, including lidocaine, esmolol, alfentanil, fentanyl, and diltiazem.[6–10]

Prostaglandin E_1 (PGE_1) has been used to maintain perioperative haemodynamic stability.[11,12] It has been shown to blunt the cardiovascular changes associated with tracheal intubation.[13] The current study was conducted to assess the ability of PGE_1 to attenuate cardiovascular responses to tracheal extubation. The effect of PGE_1 was compared with that of lidocaine, 1 $mg \cdot kg^{-1}$ *iv*. This dose of lidocaine has been shown to reduce haemodynamic changes following tracheal extubation.[6] A population of ASA I patients without cardiovascular disease was studied to ensure the safety in this initial evaluation of the effects of PGE_1 in this setting.

Methods

After obtaining institutional approval and written informed consent from all patients 80 patients (ASA physical status I) undergoing elective gynaecological or orthopaedic (lower extremity) surgery were studied. Patients were excluded if they suffered from co-existing systemic illness or were taking cardiovascular or antihypertensive medications. The patients were randomly divided, using sealed envelopes, into four groups (n = 20 each): saline (control group, PLAC), 1 $mg \cdot kg^{-1}$ lidocaine (LID), 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ PGE_1 (Prostandin®, Ono, Japan) (PGE_1LOW), or 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ PGE_1 (PGE_1MOD). The PGE_1 infusion was initiated from the end of surgery and continued until five minutes after tracheal extubation. Lidocaine was given two minutes before tracheal extubation. Double dummy technique was employed to accomplish a double-blind protocol (Table I). All patients received one drug by injection and one drug by infusion using a microinjection system (Terufusion STC-523®, Terumo, Tokyo, Japan). In the control group, saline was infused from the end of surgery and saline was injected two minutes before tracheal extubation. In the PGE_1 groups, the drug was infused from the end of surgery and saline was injected two minutes before tracheal extubation. Patients in the lidocaine group received an infusion of saline and a bolus injection of lidocaine. These medications had been prepared during each surgery by an assistant, and their identity was unknown to the anaesthetist.

The rationale for these doses and for the timing of PGE_1 (0.05 and 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ PGE_1; given from completion of surgery until five minutes after extubation) in this study was based on the following findings: (1) the use of PGE_1, approximately 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ PGE_1, is recommended to treat intraoperative hypertension;[14,15] (2) A dose of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ PGE_1, has been used to induce hypotension during cerebral aneurysm surgery[11] and mastectomy,[12] and (3) This dose has been shown to attenuate cardiovascular changes following tracheal intubation in hypertensive subjects.[12] The onset of the anti-hypertensive action of PGE_1 is obvious within five minutes of the start of infusion and values return to baseline within five minutes of the completion of administration.[15]

Premedication consisted of diazepam 4–6 mg *po* one hour before induction of anaesthesia and atropine 0.5 mg *im* 30 min before induction. An epidural catheter was placed preoperatively, but no drugs were administered via this route until final haemodynamic data had been obtained. Anaesthesia was induced with 5 $mg \cdot kg^{-1}$ thiopentone and 2 $\mu g \cdot kg^{-1}$ fentanyl and tracheal intubation was facilitated with 0.2 $mg \cdot kg^{-1}$ vecuronium *iv*. Anaesthesia was maintained with sevoflurane 1.0–2.5% (end-tidal partial pressure) and nitrous oxide 60% in oxygen. The $P_{ET}CO_2$ was maintained between 4.0 and 5.5 kPa (30 and 42 mmHg). Peripheral arterial oxygen saturation (SpO_2) and the end-tidal concentration of sevoflurane were monitored throughout anaesthesia (Capnomac Ultima®). The BP was recorded immediate-

TABLE II Demographic and haemodynamic data (mean ± SEM).

	Saline (control)	*PGE_1 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$*	*PGE_1 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$*	*Lidocaine 1 $mg \cdot kg^{-1}$*
n	20	20	20	20
Male/Female	4/16	6/14	3/17	4/16
Age (yr)	37 ± 1.5	39 ± 1.5	41 ± 1.8	38 ± 1.7
Weight (kg)	55 ± 2.0	57 ± 1.9	54 ± 2.3	58 ± 2.5
Height (cm)	161 ± 2.1	163 ± 3.0	159 ± 2.0	162 ± 3.4
Baseline				
- SBP (mmHg)	125 ± 2.9	120 ± 2.6	123 ± 2.8	121 ± 2.8
- DBP (mmHg)	79 ± 2.2	74 ± 2.1	76 ± 2.1	75 ± 2.0
- HR ($beats \cdot min^{-1}$)	73 ± 1.8	74 ± 1.9	70 ± 1.8	70 ± 1.9
Duration of anaesthesia (min)	167 ± 5.3	132 ± 5.2	120 ± 4.9	121 ± 5.2
Duration of surgery (min)	125 ± 4.9	132 ± 5.1	120 ± 5.0	121 ± 5.1
Types of surgery				
- Gynaecological	14	11	16	13
- Lower extremity	6	9	4	7

SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate. $P > 0.05$ for all variables.

ly before the induction of anaesthesia and every three minutes during anaesthesia using an automated noninvasive BP monitor with printer (Pulsemate BX-5®, Nippon Colin, Tokyo, Japan). The heart rate (HR) was monitored by electrocardiography (ECG lead II). The BP and HR were maintained between 80% and 120% of the preoperative values by increasing or decreasing the concentration of sevoflurane until the completion of surgery. Muscle relaxation was maintained with intermittent boluses (0.02 $mg \cdot kg^{-1}$) of vecuronium. After surgery, sevoflurane and N_2O were discontinued, and residual muscle relaxation was reversed with neostigmine 0.05 $mg \cdot kg^{-1}$ and atropine 0.02 $mg \cdot kg^{-1}$ *iv*. The trachea was extubated five minuetes after the administration of these drugs. Immediately before tracheal extubation, we confirmed that the concentration of end-tidal sevoflurane had decreased by 0.1% and that the patients could breathe spontaneously ($P_{ET}CO_2 < 6.6$ kPa (49.5 mmHg)) and open their eyes on command. The recovery from muscle relaxation was assessed by hand grip. Oropharyngeal secretions were aspirated prior to extubation. Immediately after tracheal extubation, 100% oxygen was given via a face mask for five minutes.

The BP and HR were then recorded every minute from the completion of surgery (i.e., the time at which the injection of neostigmine and atropine was administered). The systolic BP (SBP), diastolic BP (DBP), and HR measured at the end of surgery served as baseline values. Haemodynamic data obtained from three minutes after the injection of the neostigmine-atropine mixture (i.e., two minutes before extubation) until 10 min after extubation were analyzed for cardiovascular changes associated with emergence from anaesthesia and tracheal extubation. Peak SBP, DBP, and HR values observed during tracheal extubation and emergence from anaesthesia were also recorded for the calculation of maximum percent changes. Values for SBP, DBP, and HR immediately before the induction of anaesthesia, at completion of surgery, two and one min before tracheal extubation, at tracheal extubation, and 1, 5, and 10 min after tracheal extubation were compared in the four groups. These values were also compared with baseline values (at completion of surgery) within the individual study groups. The haemodynamic data were also recorded immediately after return to the ward from the operating room (approximately 20 min after tracheal extubation). The quality of tracheal extubation was evaluated on a five-point rating scale (1 = no coughing or straining, 2 = very smooth, minimal coughing, 3 = moderate coughing, 4 = high degree of coughing or straining, and 5 = poor extubation, very uncomfortable).[9]

Twenty patients per group are sufficient to detect large difference (siginificant difference d = 0.8) with $\alpha = 0.05$ and power $1\text{-}\beta = 0.8$. Data are expressed as mean ± SEM. Statistical analysis was performed using a two-way (time and group) analysis of variance followed by Bonferroni modification of t test for parametric data, and using the Kruskal-Wallis test and chi-squared test for nonparametric (distribution) data. $P < 0.05$ was deemed significant.

Results

No differences were observed among the four groups with respect to weight, age, sex, or duration of anaesthesia, or with respect to preoperative SBP, DBP, or HR. (Table II)

The SBP, DBP, and HR in the control group increased in association with tracheal extubation.

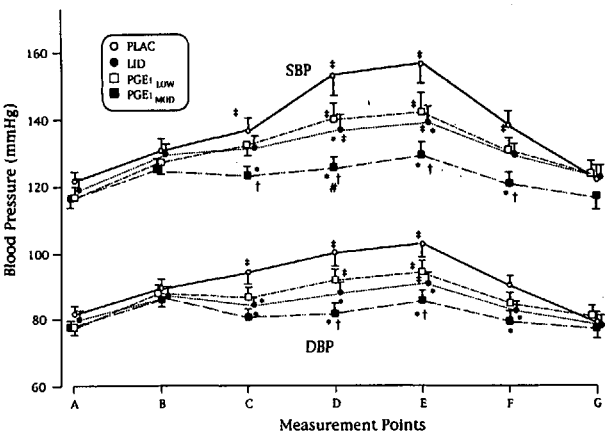

FIGURE 1 Changes in systolic and diastolic blood pressure (mean ± SEM) during anaesthesia. SBP: systolic blood pressure, DBP: diastolic blood pressure. PLAC: saline (control group), LID: Lidocaine group, PGE_1LOW: PGE_1 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$, PGE_1MOD: PGE_1 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Open circles: PLAC; closed circles, LID; open squares: PGE_1LOW; closed squares: PGE_1MOD. $^*P < 0.05$ vs PLAC, $\#P < 0.05$ for PGE_1MOD vs LID, $P < 0.05$ for PGE_1MOD vs PGE_1LOW, $P < 0.05$ vs basal value within each group. Measurement points; A: completion of surgery (beginning of infusion of PGE_1 or saline), B: two minutes before tracheal extubation (administration of lidocaine), C: one minutes before tracheal extubation, D: tracheal extubation, E: one min after tracheal extubation, F: five minutes after tracheal extubation, G: 10 min after tracheal extubation.

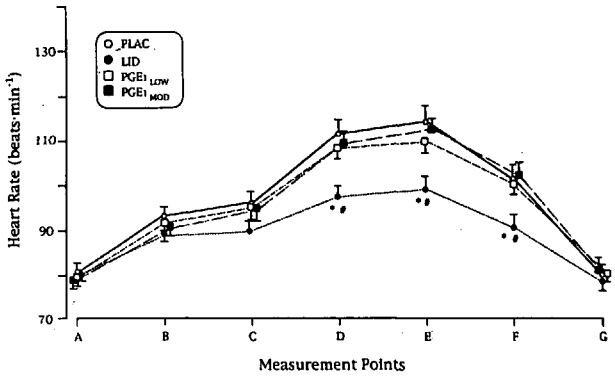

FIGURE 2 Changes in heart rate (mean ± SEM) during anaesthesia. PLAC: saline (control group), LID: Lidocaine group, PGE_1LOW: PGE_1 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ PGE_1MOD: PGE_1 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Open circles: PLAC; closed circles, LID; open squares: PGE_1LOW; closed squares: PGE_1MOD. $^*P < 0.05$ vs PLAC, $\#P < 0.05$ for LID vs PGE_1MOD. The HR at points B to F were $P < 0.05$ vs basal value (within each group) in all groups. Measurement points; A: completion of surgery (beginning of infusion of PGE_1 or saline), B: two minutes before tracheal extubation (administration of lidocaine), C: one minute before tracheal extubation, D: tracheal extubation, E: one minute after tracheal extubation, F: five minutes after tracheal extubation (completion of infusion of PGE_1 or saline), G: 10 min after tracheal extubation.

(Figures 1 and 2) Although lidocaine successfully attenuated these increases, PGE_1 at the dose of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ PGE_1 blunted the hypertension but not the tachycardia. The maximum percent change of BP was less in groups PGE_1MOD and LID, compared with groups PGE_1LOW and PLAC (Figure 3).

Fewer patients who received PGE_1MOD experienced SBP > 150 mmHg or DBP > 90 mmHg. However, a similar number of patients had HR > 100 beats $\cdot$ min^{-1} in groups PGE_1MOD and the PLAC. Lidocaine reduced the number of patients with SBP > 150 mmHg or HR > 100 beats $\cdot$ min^{-1} (Table III).

No patients suffered from laryngeal spasm after extubation. Of the patients in groups PLAC, LID, PGE_1LOW, and PGE_1MOD, the numbers who coughed or strained were 20, 11, 20, and 20, and extubation quality scores (median (range)) were 3 (2–5), 2 (1–3), 3 (2–5), and 3 (2–5), respectively. Lidocaine (1 mg $\cdot$ kg^{-1}) suppressed coughing and straining compared with the other three treatments ($P < 0.05$).

No patients in the PGE_1 groups developed profound hypotension (SBP < 80 mmHg16) severe enough to require pressor drugs during tracheal extubation or in the ward. Seven patients in the PGE_1LOW and 11 in the

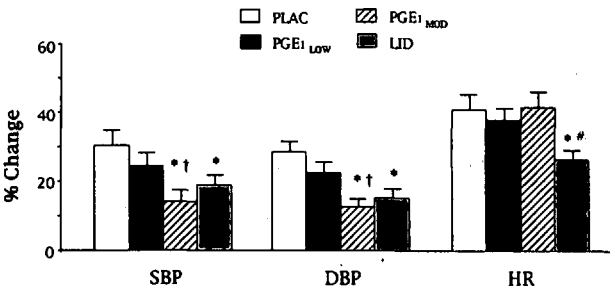

FIGURE 3 Maximum percent changes in systolic and diastolic blood pressure and heart rate (mean ± SEM) from levels at completion of surgery to levels associated with tracheal extubation in the four groups ($n = 20$ each). SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate. PLAC: saline (control group), LID: lidocine 1 mg $\cdot$ kg^{-1}, PGE_1LOW: PGE_1 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$, PGE_1MOD: PGE_1 0.1 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Open columns: PLAC, closed columns: PGE_1LOW, striped columns: PGE_1MOD, dotted columns: LID. $^*P < 0.05$ vs PLAC, $\#P < 0.05$ for LID vs PGE_1MOD, $P < 0.05$ for PGE_1MOD vs PGE_1LOW.

PGE_1MOD groups had phlebitis; a redness of the skin at the infusion site, but this disappeared within a few hours without any pharmacological treatment.

Discussion

We have confirmed that tracheal extubation caused

TABLE III Number of patients demonstrating hypertension and tachycardia upon extubation after treatment ($n = 20$ for each group).

	Systolic blood pressure >150 mmHg	*Diastolic blood pressure >90 mmHg*	*Heart rate >100 beats · min^{-1}*
Saline (control)	14	16	18
Lidocaine 1 mg · kg^{-1}	6*	10	9*†‡
Prostaglandin E_1 0.05 μg · kg^{-1} · min^{-1}	8	12	17
Prostaglandin E_1 0.1 μg · kg^{-1} · min^{-1}	2*†	8*	18

*Significantly smaller than control (saline) group. $P < 0.05$.
†Significantly smaller than prostaglandin E_1 0.05 μg · kg^{-1} · min^{-1} group. $P < 0.05$.
‡Significantly smaller than prostaglandin E_1 0.1 μg · kg^{-1} · min^{-1} group. $P < 0.05$.

hypertension and tachycardia, and that these haemodynamic changes were attenuated by lidocaine 1 mg · kg^{-1} *iv*. We have found that the PGE_1MOD exerted similar effects on the increase in BP to LID, although it failed to blunt the tachycardia. During and after tracheal extubation plasma concentrations of catecholamines (CA) are reported to increase.[17] Although the precise mechanism responsible for tachycardia and hypertension following tracheal extubation is unknown, it is conceivable that these haemodynamic changes may be associated with the release of CA that occurs during this stressful period. However, PGE_1 at doses used in the clinical setting is unlikely to suppress CA release.[18] This suggests that the effectiveness of PGE_1 in controlling BP is due to the direct vasodilatory property of the drug, but not to its inhibition of CA release.

Tracheal extubation irritates airways, causing coughing or straining, both of which increase BP and HR. The number of patients who experienced coughing or straining was less in LID than in PLAC and PGE_1 groups, in whom the incidence was similar. Although PGE_1 at either of the doses used failed to attenuate laryngeal irritation, the drug in the moderate dose successfully blunted the hypertensive changes associated with tracheal extubation. A combination of lidocaine and PGE_1 may attenuate haemodynamic changes to more tolerable levels than either drug administered alone, since the mechanisms by which these drugs attenuate hypertension or tachycardia, appear to be different. The effects of a combination of these two drugs in the same setting deserve further studies.

There is growing awareness of medical economy. The costs of lidocaine and PGE_1 are about 0.5 and 30$ (Canada) at the doses used in the current study. As PGE_1 is so expensive its use only for this purpose might not be practical. However, PGE_1 in moderate dose attenuated the increase in BP as effectively as lidocaine. Thus, when PGE_1 was prepared and used intraoperatively, the drug should be applied to reduce the increase in BP during emergence from anesthesia.

Various investigators have reported the cardiovascular responses to tracheal extubation after coronary artery surgery in patients with CAD. One study has indicated that HR, BP, cardiac index, systemic vascular resistance index, pulmonary artery pressure, plumonary artery occlusion pressure, and pulmonary vascular resistance index increased considerably in association with tracheal extubation.* In patients with CAD, myocardial ischaemia may occur during tracheal extubation,[19,20] and the occurrence of intraoperative ischaemia is associated with a higher incidence of perioperative myocardial infarction. Since HR is a major controllable determinant of myocardial oxygen balance,[21] the failure of PGE_1 to exert a suppressive effect on tachycardia may not justify its use in this setting.

In conclusion, in ASA I patients, infusion of 0.1 μg · kg^{-1} · min^{-1} PGE_1 PGE_1 0.1 during emergence from anaesthesia and tracheal extubation is a simple and effective method of blunting the hypertensive response to tracheal extubation. This suppressive effect of PGE_1 was comparable with that of lidocaine 1 mg · kg^{-1} *iv*. However, further studies are required to evaluate the benefit/risk ratio of PGE_1 in comparison with other drugs when used for the purpose of attenuating the haemodynamic changes associated with extubation in patients with CAD and cerebrovascular disease.

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