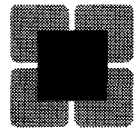

The hemodynamic effects of intravenous labetalol for postoperative hypertension

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■ Hemodynamic data were analyzed from 25 courses of intravenous pulse labetalol therapy for postoperative hypertension in 12 patients after major vascular surgeries. The hemodynamic determinations were obtained an average of 15 minutes after a therapeutic total dose of 10–120 mg of labetalol (mean, 37.5 mg). The mean arterial pressure (MAP) decreased an average of 27 mmHg or 20% after intravenous labetalol. This normalization of the postoperative hypertension was associated with a 19% increase in cardiac output (CO) and cardiac index (CI) (CO mean increase of 0.58 L/min and CI increase of 0.31 L/min/m^2). Commensurate with this decrease in MAP and increase in CO was an average decrease in systemic vascular resistance (SVR) of 625 dyne/sec/cm^{-5} or 25%. The pulmonary vascular resistance decreased 15 dyne/sec/cm^{-5} or 4%. The heart rate decreased 9 beats per minute or 10% and the left ventricular stroke work improved by 9% or 1.6 g/m^2/beat while the right ventricular stroke work increased by 33% or 2.8 g/m^2/beat. The hemodynamic responses to intravenous labetalol in these patients were all beneficial, and there were no adverse effects secondary to the pulse doses of labetalol. Labetalol appears to be safe and efficacious for the treatment of postoperative hypertension in patients undergoing major vascular surgery.

□ INDEX TERMS: HYPERTENSION; LABETALOL □ CLEVE CLIN J MED 1989; 56:29–34

LABETALOL is a combined selective alpha$_1$-adrenergic and nonselective beta-adrenergic receptor blocking agent that is effective for the treatment of both acute and chronic hypertension.[1,2] The ratio of its competitive alpha-blockade to beta-blockade after intravenous administration is approximately 1:7.[3]

We studied the hemodynamic effects of postoperative labetalol in 12 patients who had undergone major vascular surgery and already had Swan-Ganz catheters in place. In addition to its effects on blood pressure (BP), we evaluated its effects on cardiac output (CO), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), intrapulmonary shunt, heart rate (HR), and left and right ventricular stroke work (LVSW and RVSW). The hemodynamic determinations were obtained an average of 15 minutes after a therapeutic total dose of 10–120 mg of labetalol. The therapeutic dose of labetalol was the cumulative dose necessary to obtain an appropriate BP response, defined as a diastolic BP of ≤ 90 mmHg for at least 5 minutes. Labetalol was administered in 10–20-mg bolus pulses until the desired BP response was obtained.

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TABLE 1
AVERAGE HEMODYNAMIC EFFECTS OF INTRAVENOUS LABETALOL IN 12 PATIENTS STATUS POST MAJOR VASCULAR SURGERY

Hemodynamic parameter	Average absolute change	Average percent change
Cardiac output (L/min)	+0.58	+19%
Cardiac index (L/min/m^2)	+0.31	+19%
Systemic vascular resistance (dyne/sec/cm^{-5})	-625	-25%
Pulmonary vascular resistance (dyne/sec/cm^{-5})	-15	-4%
Intrapulmonary shunt (%)	0	0
Heart rate (bpm)	-9	-10%
Pulmonary capillary wedge pressure (mmHg)	-1	-5%
Central venous pressure (mmHg)	-1	-10%
Left ventricular stroke work (g/m^2/beat)	+1.6	+9%
Right ventricular stroke work (g/m^2/beat)	+2.8	+33%
Mean arterial blood pressure (mmHg)	-27	-20%

METHODS

Twelve patients (nine men, three women) with an average age of 72 years (range, 55–83 years), who had undergone major vascular surgery (abdominal aortic aneurysmectomy with aorto-bifemoral or aorto-bi-iliac grafts in all 12, three with additional implant grafts [one superior mesenteric artery, one inferior mesenteric artery, and one left renal]), were studied. Each of the patients already had a Swan-Ganz catheter in place and was eligible for study in the immediate postoperative period if significant hypertension developed, defined as a systolic BP ≥ 200 mmHg and/or diastolic BP of ≥ 100 mmHg. Ten of the 12 patients had been receiving antihypertensive therapy preoperatively. All patients were still intubated and required mechanical ventilation at the time of study.

Because a number of factors such as pain, hypothermia, and hypovolemia can produce postoperative hypertension (typically a wide-pulse-pressure hypertension) that does not require antihypertensive drugs, these contributing factors were treated first. Only patients who remained hypertensive after morphine sulfate for pain, external warming to normothermia, and correction of hypovolemia were treated with labetalol.

Exclusion criteria for the study included acute or uncompensated right-sided heart failure, sinus bradycardia (HR < 50 bpm), second- or third-degree atrial-ventricular heart block, and pregnancy.

No concomitant antihypertensive therapy was used during the labetalol therapy phase. If patients were admitted to the surgical intensive care unit from the operating room while receiving a nitroprusside or nitroglycerine infusion, the infusion was discontinued for a minimum of 15 minutes before initiating labetalol therapy. Many patients had received mannitol intraoperatively, but did not receive mannitol or diuretics during the study.

In all patients, ECG and arterial BP were recorded continuously throughout the study period. In addition, complete hemodynamic profiles were recorded, including CO, pulmonary artery pressures, central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), and arterial and mixed venous blood gases an average of 15 minutes (range, 5–30 minutes) after an appropriate BP response to labetalol was obtained. Hemodynamic profiles were remeasured at 4-hour intervals after response or 15 to 30 minutes after additional 20–40-mg doses of labetalol.

Labetalol therapy consisted of an initial dose of 10 mg by slow intravenous injection over a two-minute period. Additional 10–20-mg dosages of labetalol were administered at 10-minute intervals until a supine diastolic BP ≤ 90 mmHg was achieved or until a total of 300 mg of labetalol had been administered. Once an appropriate BP response was obtained (diastolic BP < 90 mmHg for five minutes), hemodynamic profiles were obtained. If the diastolic BP subsequently rose by 10 mmHg on two consecutive measurements five minutes apart, the dose of labetalol could be repeated, but the total dose of labetalol in any 24-hour period could not exceed 300 mg. Patients who did not reach a diastolic BP of 90 mmHg or less were considered treatment failures and alternative antihypertensive therapy was initiated.

RESULTS

All 12 patients responded to labetalol therapy with an acceptable BP response. Patients received an average of 100 mg of labetalol over 24 hours for BP control; 40 mg was the average dose for initial sustained therapeutic response. The hemodynamic effects of the intravenous labetalol doses are shown in *Table 1*. A total of 25 hemodynamic profiles were obtained on the 12 patients, an average of 15 minutes after cumulative 10–120-mg intravenous labetalol doses.

All of the hemodynamic changes due to intravenous labetalol were beneficial in this postoperative group of elderly patients who underwent major vascular surgery. The 20% reduction in mean arterial BP was associated with a minimal decrease in HR of 9 beats per minute (10%), no change in intrapulmonary shunt, and a clini-

cally inconsequential 1-mmHg decrease in both PCWP and CVP. CO and CI both improved by 19%, with a 9% increase in LVSW and a 33% improvement in RVSW. Commensurate with the decrease in BP and improvement in CO was a 25% decrease in SVR and a 4% decrease in PVR.

There were no adverse hemodynamic or pulmonary responses to labetalol therapy in any of the patients despite the coexistence of major cardiovascular disease in all patients and the presence of chronic obstructive pulmonary disease (COPD) in seven.

Representative strip chart recordings of HR, BP, pulmonary artery pressure, and CVP in two patients before, during, and after an intravenous dose of labetalol are shown in *Figures 1* and *2*. The time of onset of action and time to peak effect are clearly shown in these recordings. The onset of action was 10–20 seconds following completion of injection with a peak effect at 30–60 seconds in these two patients.

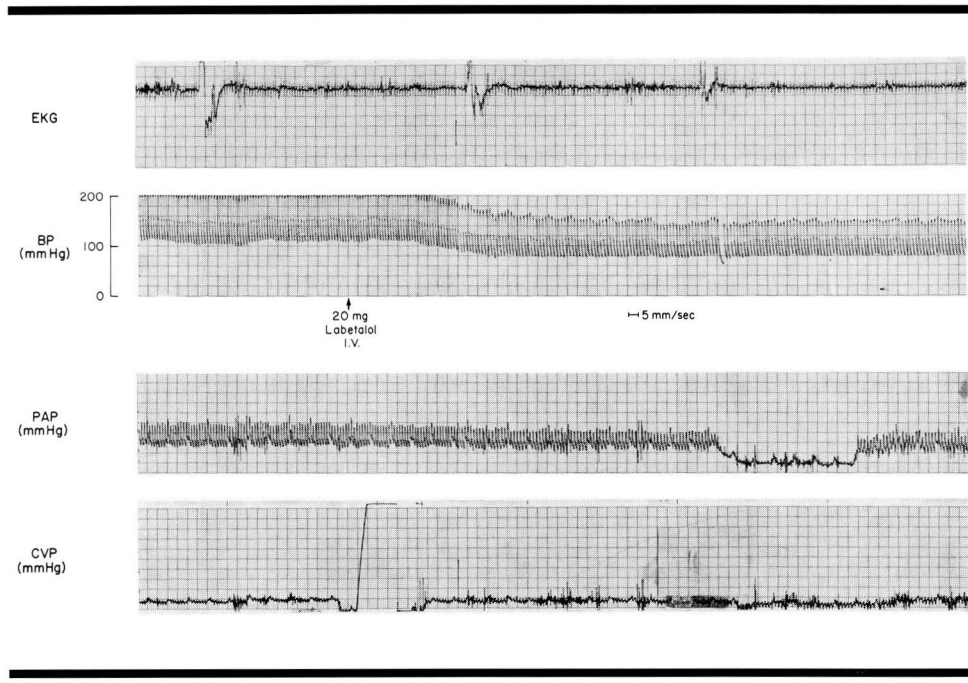

FIGURE 1. A four-channel continuous strip-chart recording of heart rate (*HR*), blood pressure (*BP*), pulmonary artery pressure (*PAP*), and central venous pressure (*CVP*) before, during, and after intravenous labetalol treatment of postoperative hypertension. The BP before labetalol therapy was 250/120 mmHg. The labetalol was administered in the CVP line, as evidenced by the interruption in the CVP waveform tracing. The onset of action of the labetalol was approximately 10 seconds after completion of the injection. A peak effect occurred approximately 30 seconds after the dose of 20 mg of labetalol. The decrease in PAP and loss of waveform later in the tracing occurred at the time of balloon-inflation for measurement of pulmonary capillary wedge pressure.

DISCUSSION

Early postoperative hypertension is a common occurrence in patients after major vascular surgical procedures. Although pain, hypovolemia, hypercarbia, anxiety, and hypothermia can all contribute to the development of a wide-pulse-pressure hypertension, many of these patients have pre-existing chronic hypertension and arteriosclerotic cardiovascular disease. Hypertension on emergence from anesthesia can also result from the sympathoneuronal release of norepinephrine with a resultant increase in SVR.[4]

The incidence of significant coronary artery disease in patients with abdominal aortic aneurysms may be as high as 95%.[5] The development of postoperative hypertension warrants immediate assessment and appropriate treatment to reduce the risks of myocardial infarction, arrhythmias, congestive heart failure, stroke, bleeding, or other end-organ damage. Acute myocardial infarction is a common occurrence during aortic surgery and is a major cause of late death among patients undergoing major vascular surgery.[6,7] A safe balance between CO, myocardial oxygen demand, and arterial BP must be maintained perioperatively, especially in patients with underlying cardiovascular disease.

Elevations of HR and systolic arterial BP in patients with coronary artery disease can result in an unfavorable ratio of myocardial oxygen supply to demand with resultant development of myocardial ischemia.[8] Elevations of left ventricular diastolic pressure may also impair diastolic coronary blood flow.[9] Traditionally, acute postoperative hypertension is managed by carefully monitored intravenous infusions of sodium nitroprusside. Propranolol is often used in conjunction to prevent reflex tachycardia. Sodium nitroprusside is an effective but costly form of therapy because of the close bedside nurs-

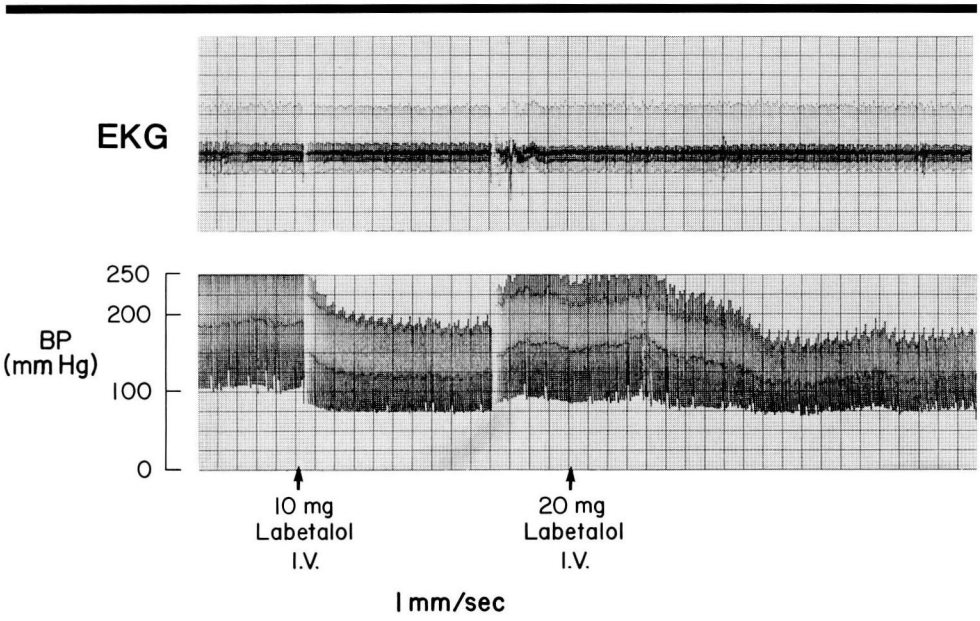

FIGURE 2. A two-channel recording of heart rate (*HR*) and blood pressure (*BP*) in a different patient during treatment of postoperative hypertension with 10 mg and then 20 mg of labetalol. The BP prior to the initial 10-mg dose of labetalol therapy was 280/110 mmHg and came down to 180/75 mmHg. The recording was interrupted after the 10-mg dose. A continuous recording shows a BP of 250/90 mmHg prior to the 20-mg dose; the effect of labetalol became obvious approximately 20 seconds afterward and reached a maximum antihypertensive effect approximately 60 seconds later, when the BP came down to 160/75 mmHg.

ing supervision required to monitor continuous intravenous infusions.[10,11] A parenteral antihypertensive agent that offers the alternative of only periodic intravenous injections is desirable if it is safe and effective in controlling postoperative hypertension.

Labetalol is an antihypertensive agent with both alpha- and beta-adrenergic receptor blocking properties.[12] The alpha- to beta-blocking potency ratio of intravenous labetalol is approximately 1:7. In contrast to agents possessing only beta-blocking activity, labetalol immediately and significantly lowers SVR by blocking alpha-adrenergic receptors with direct vasodilation, without significant reflex effects on HR because of its beta-adrenoceptor blockade.[13] The plasma half-life of labetalol is approximately 3.5 to 4.5 hours, but the pharmacologic effect of this agent outlasts its plasma half-life.[14] After an intravenous injection of labetalol, the full antihypertensive effect is apparent within 5–10 minutes although in our patients a peak effect was often discernable in one minute or less after completion of injection.[15] Intravenous doses of 20–80 mg appear effective in bringing about acute and significant reductions in both systolic and diastolic BP.[15] In some patients, especially those without a history of hypertension, a dose of 10 mg may be sufficient, as was seen in some of our patients (*Figure 2*) (*Table 2*).

Labetalol is an approved antihypertensive agent in the United States. Extensive experience with intravenous labetalol has demonstrated its safety and effectiveness in the control of severe hypertension, hypertensive urgencies, and hypertensive emergencies, but data on its use for postoperative hypertension are limited.[16] We have demonstrated that labetalol is both an effective and safe treatment for postoperative hypertension in vascular surgery patients. The hemodynamic effects of therapy with labetalol were all beneficial. Effective control of postoperative hypertension was associated with a 25% reduction in SVR, a 19% increase in CI, a 33% increase in RVSW, a 9% improvement in LVSW, and a 10% decrease in HR. Despite the presence of cardiovascular disease in all of the patients and COPD in 7 patients, there were no adverse hemodynamic or pulmonary effects from labetalol therapy. Labetalol is a weaker beta-adrenergic blocking drug than propranolol; propranolol has 4–6 times the $beta_1$-blocking potency and 11–17 times the $beta_2$-blocking potency.[17] Labetalol is devoid of intrinsic sympathomimetic activity at $beta_1$-adrenoceptors and may even possess intrinsic agonist activity at $beta_2$-adrenoceptors.[18,19] Alternatively, alpha-blockade may reduce the risk of bronchospasm in the presence of beta-blockade.[18] Labetalol has been shown to reduce myocardial oxygen consumption and improve coronary hemodynamics in patients with coronary artery disease.[20,21]

A recent report[22] on the use of labetalol by continuous intravenous infusion for postoperative hypertension in six patients after aorto-femoral bypass surgery found a 32% ± 11% decrease in HR, but a 26% ± 15% decrease in CI. This fall in CI contradicts our results, but may be explained by the fact that their patients were studied an

TABLE 2
HEMODYNAMIC PARAMETERS BEFORE AND AFTER LABETALOL THERAPY FOR POSTOPERATIVE HYPERTENSION IN 12 PATIENTS AND 25 TREATMENT COURSES

Patient	Labetalol Dose*	Time (min)	MAP (mmHg)	HR (bpm)	CO (Lpm)	CI (L/min/m²)	SVR (dyne/sec/cm⁵)	PVR (dyne/sec/cm⁵)	LVSW (g/m²/beat)	RVSW (g/m²/beat)
Normal ranges			(80–105)	(60–90)	(3.5–7.0)	(2.5–4.4)	(800–1200)	(50–100)	(60–80)	(10–15)
1a	20 mg	pre	130	80	7.8	5.4	1197	143	126	27
		30 post	104	64	4.5	3.1	1668	403	72	21
1b	10 mg	pre	104	90	4.3	3.0	1730	316	57	14
		15 post	88	83	7.8	5.4	764	175	79	30
2a	20 mg	pre	140	83	2.5	1.4	4320	416	34	5.8
		15 post	117	72	3.3	1.8	2763	218	43	4.4
2b	20 mg	pre	133	83	2.5	1.4	4320	416	34	5.8
		10 post	112	69	2.7	1.5	3278	270	35	3.7
2c	20 mg	pre	140	83	2.2	1.2	3678	285	28	3.1
		20 post	103	83	5.1	2.8	1956	236	62	8.3
3a	40 mg	pre	140	84	5.2	3.1	1903	108	73	18
		15 post	118	72	6.2	3.6	1357	142	86	22
3b	80 mg	pre	140	84	5.2	3.0	1903	108	73	18
		15 post	130	69	5.9	3.5	1567	175	95	23
4	20 mg	pre	140	88	4.4	2.4	2500	187	77	20
		20 post	120	75	5.0	2.7	1700	100	83	22
5a	60 mg	pre	138	83	3.8	2.1	2590	126	51	4.2
		30 post	110	81	5.2	2.9	1560	153	57	4.6
5b	40 mg	pre	140	83	3.8	2.1	2590	126	51	4
		15 post	100	77	5.8	3.2	1278	181	62	15
6a	80 mg	pre	140	64	3.8	1.9	2220	210	52	9.5
		5 post	116	72	4.3	2.2	1865	190	50	9.4
6b	120 mg	pre	120	74	4.4	2.2	1828	200	52	9.5
		15 post	103	75	3.9	2.0	2100	220	50	9.3
7a	40 mg	pre	140	100	3.8	2.2	2500	250	55	10
		20 post	120	90	4.4	2.6	1700	200	59	12
7b	40 mg	pre	140	100	3.8	2.2	2500	250	55	10
		20 post	110	92	4.5	2.5	1800	200	60	13
8a	40 mg	pre	160	85	6.6	3.3	1900	159	88	14
		10 post	105	77	7.6	3.8	1100	168	76	18
8b	40 mg	pre	160	85	6.5	3.3	1878	160	90	14
		20 post	90	94	8.0	4.0	812	140	56	18
9	10 mg	pre	120	84	8.3	4.1	1140	116	85	23
		10 post	98	70	8.0	4.0	830	170	80	33
10a	20 mg	pre	145	86	7.0	4.1	1570	193	87	12
		5 post	120	78	5.8	3.4	1500	100	75	12
10b	20 mg	pre	144	85	5.8	3.4	1600	96	75	12
		10 post	128	76	5.0	2.9	1880	160	70	11
11a	20 mg	pre	120	71	3.6	2.1	2500	160	52	9
		10 post	86	61	4.9	2.9	1290	115	59	12
11b	40 mg	pre	120	70	3.6	2.1	2500	160	52	9
		20 post	83	60	4.8	2.8	1280	120	59	12
11c	40 mg	pre	105	60	4.8	2.8	1280	120	59	12
		20 post	85	55	4.9	2.9	1100	115	59	13
11d	20 mg	pre	125	60	4.8	2.8	1280	120	56	12
		10 post	105	50	5.3	3.1	1150	110	70	15
12a	40 mg	pre	115	100	5.0	2.8	1700	160	46	10
		5 post	98	76	4.9	2.7	1500	163	51	13
12b	40 mg	pre	120	100	4.9	2.7	1500	163	46	13
		10 post	85	73	5.0	2.8	1200	160	47	14

*To achieve therapeutic response.
MAP = mean arterial pressure; *HR* = heart rate; *CO* = cardiac output; *CI* = cardiac index; *SVR* = systemic vascular resistance; *PVR* = pulmonary vascular resistance; *LVSW* = left ventricular stroke work index; *RVSW* = right ventricular stroke work index.

average of 15 hours postoperatively, were all extubated, and were receiving epidural morphine analgesia. Most of their patients had high-normal to supra-normal cardiac indexes prior to labetalol therapy. Our patients received labetalol in the immediate postoperative period, were all intubated, and most had low-normal to sub-normal car-

diac indexes prior to labetalol therapy. Our patients were also considerably older, with a mean age of 72 years compared with 57 years. The older age of our patients may have resulted in less beta-adrenergic receptor sensitivity and therefore less effect on HR. However, Leslie et al,[16] in their study of intravenous labetalol for treatment of postoperative hypertension, found good control of systolic and diastolic hypertension and minimal changes in HR in patients with an average age of 57 years.[16]

In our series, patients with initially low cardiac indexes had improved cardiac function after labetalol therapy. In the one patient with an initially high CI, the CI fell into the normal range after the first treatment course with labetalol and then returned to supranormal levels after the second course of labetalol therapy (Patient 1, *Table 2*).

Labetalol appears to be a safe and efficacious drug for the treatment of postoperative hypertension in patients who have undergone major vascular surgery and offers an attractive and effective alternative to BP control by continuously monitored intravenous infusions.

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