Hemodynamic and Blood-gas Effects of Innovar in Patients with Acquired Heart Disease

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The effects of Innovar on hemodynamics and blood gases were studied in 18 adult patients with advanced cardiac disease during analgesia and sedation for angiocardiography. No significant changes in cardiac index or rate, stroke volume, stroke work, or left ventricular systolic and diastolic pressures were observed. Femoral systolic pressure decreased, on the average, from 152 to 139 mm Hg; femoral diastolic pressure, from 74 to 67 mm Hg; mean femoral pressure, from 100 to 91 mm Hg. Systemic vascular resistance decreased from 40.4 to 35.8 units, while pulmonary resistance did not change. $Paco_2$ increased from 35 to 40 mm Hg, whereas Pa_{O_2} decreased from 76 to 57 mm Hg. All these changes were significant. (Key words: Innovar; Hemodynamic effects; Blood gases; Cardiac patients; Peripheral resistance.)

NEUROLEPTANALGESIA with Innovar, a combination of droperidol and fentanyl in a 50:1 ratio (2.5:0.05 mg/ml), has been advocated for use in anesthesia for cardiac surgery,[1] in poor-risk patients,[2] and as premedication.[3] The advantages put forth include cardiovascular stability and a relative absence of undesirable side effects.[4] These conclusions have been derived either from clinical impressions[2] or from hemodynamic studies of patients who had no known cardiovascular disease.[4,5] Because the drug is recommended specifically for patients undergoing open-heart surgery and for poor-risk patients, we have assessed the acute hemodynamic and respiratory effects of Innovar on patients with advanced cardiac disease.

We gave Innovar to 18 adult patients during diagnostic cardiac catheterization for analgesia and sedation during angiocardiography and evaluated its effects on hemodynamics and blood gases. All patients were moderately or severely incapacitated, in class III or IV according to the New York Heart Association Classification.

Methods

The ages of the patients (11 men and seven women) ranged from 23 to 78 years. Sixteen patients had valvular disease (table 1): six of these had aortic stenosis and three, mitral stenosis. Two patients had cardiomyopathies of unknown cause. Both of these patients had left ventricular end-diastolic pressures above 12 mm Hg. All patients had fasted overnight. None had received premedication. As part of the diagnostic procedure, a catheter was manipulated into the left ventricle of each patient via the brachial artery and an indwelling needle was placed in the femoral artery. Catheters and needles were inserted using local anesthesia (1 per cent lidocaine without epinephrine).

Using a strain-gauge (Statham Model P23b), left ventricular and femoral arterial pressures were recorded simultaneously by a galvanometer-oscillograph assembly and a visual recorder (Visicorder, Model 1012). Pulmonary arterial pressures of 13 patients were measured simultaneously with separate catheters. In nine patients, cardiac outputs were measured by the indicator-dilution technique of Hamilton.[6] Indocyanine green injected into the left ventricle was sampled from the femoral artery. In the other nine patients, cardiac outputs were determined by the direct Fick method because of significant distortions of the disappearance slopes of the dye curves. Heart rate was obtained from the electrocardiogram. With the patient breathing ambient air, Pa_{O_2}, pH,

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TABLE 1. Types of Cardiac Disease* in 18 Patients Undergoing Cardiac Catheterization

Patient	Aortic Valve		Mitral Valve		Tricuspid Valve, Insufficiency	Cardiomyopathy
	Stenosis	Insufficiency	Stenosis	Insufficiency		
1		++				
2						+
3				++		+
4		++	++			
5				+++		
6	++					
7				+++		
8	++	+				
9				+++	+	
10	+		++	++		
11				+++	+	
12	+++				++	
13						+
14	+++					
15				+++		
16	+++					
17				++		
18			+++			

* Severity: mild +, moderate ++, severe +++.

and Pa_{CO_2} in femoral arterial blood were determined, using electrodes (Instrumentation Laboratories) maintained at 37 C. Oxygen consumption was determined by analysis of expired air collected for three minutes in a Douglas bag.

After completion of control measurements, Innovar was given intravenously over a three-minute period, in doses that ranged from 1 ml/23 kg to 1 ml/34 kg of body weight, depending upon the condition of the patient. Total amounts averaged 2.8 ml (range 2 to 3.5 ml). Innovar's peak respiratory effects occur about ten minutes after administration,[5] and previous observations in our laboratory had suggested that the peak cardiovascular changes occurred at approximately the same time. Therefore, a second set of measurements was made ten minutes after the injection of Innovar. After completion of these measurements, angiocardiography was carried out with contrast medium (Renovist), 1 to 1.5 ml/kg body weight.

Systemic and pulmonary resistances were calculated according to the formula:

$$\text{Units} = \frac{\text{mean pressure (mm Hg)}}{\text{flow } \left(\frac{\text{l/min}}{\text{m}^2}\right)} \quad (1)$$

Left ventricular stroke work was calculated by the formula:

$$\text{LVSW (gm-m)} = (\text{LVSP} - \text{LVEDP}) \times \text{SV} \times 0.0144 \quad (2)$$

LVSP is mean left ventricular systolic pressure obtained by planimetric integration, LVEDP is left ventricular end-diastolic pressure, and SV is stroke volume obtained from cardiac output and heart rate. The factor 0.0144 is a constant that corrects for density of blood and for the conversion of mm Hg to cm H_2O and cm to meters, thus allowing stroke work to be expressed in conventional units. Paired data (before and ten minutes after Innovar) were analyzed by Student's t test, with $P < 0.05$ taken as the level of significance.

Results

Results are summarized in tables 2, 3, and 4. Mean cardiac index was unaltered, 2.8 ± 0.09 l/min/m² before and after Innovar. Left ventricular systolic and end-diastolic pressures, stroke volume, and heart rate did not change significantly. Although stroke work decreased in 13 of 18 patients, mean values were not significantly changed, but systemic systolic, diastolic, and mean pressures decreased signifi-

TABLE 2. Changes in Hemodynamics after Administration of Innovar

Patient	Femoral Arterial Systolic Pressure (mm Hg)		Femoral Arterial Diastolic Pressure (mm Hg)		Left Ventricular Systolic Pressure (mm Hg)		Left Ventricular End-diastolic Pressure (mm Hg)		Mean Femoral Arterial Pressure (mm Hg)		Pulmonary Trunk Systolic Pressure (mm Hg)		Pulmonary Trunk Diastolic Pressure (mm Hg)		Cardiac Index (l/min/m²)		Stroke Volume (ml)		Heart Rate (beats/min)	
	Control	10 Min*	Control	10 Min	Control	10 Min	Control	10 Min	Control	10 Min	Control	10 Min	Control	10 Min	Control	10 Min	Control	10 Min	Control	10 Min
1	180	152	58	45	170	148	17	10	99	81	—	—	—	—	2.7	3.3	70	77	66	66
2	158	144	85	72	142	124	17	22	109	96	—	—	—	—	3.7	3.8	82	91	84	78
3	92	107	55	55	115	115	21	24	67	72	26	32	11	10	3.1	2.2	69	54	70	65
4	173	177	65	66	162	176	12	13	101	103	32	35	14	11	3.4	3.4	80	110	80	58
5	127	115	78	68	104	95	20	15	94	84	60	60	35	24	1.4	1.4	23	26	96	84
6	170	182	80	83	224	243	15	23	110	116	—	—	—	—	2.6	2.9	69	75	72	75
7	168	175	78	80	144	152	24	21	108	112	102	99	42	33	2.4	2.3	70	60	66	72
8	178	120	66	53	212	174	38	12	103	75	36	38	15	6	3.4	3.1	88	82	78	78
9	122	119	75	70	118	113	30	28	91	86	65	77	38	45	1.8	2.1	49	56	78	78
10	203	184	105	84	220	195	15	15	138	117	52	38	28	19	3.9	3.4	79	69	72	72
11	130	125	70	75	103	103	20	20	90	92	78	—	40	—	2.1	1.8	76	65	54	54
12	133	125	58	58	192	190	20	20	83	80	55	61	20	25	1.7	1.5	50	36	54	66
13	95	110	55	60	87	96	22	18	68	76	45	44	25	20	4.3	3.9	121	77	68	95
14	156	109	57	42	175	147	14	10	90	64	—	—	—	—	2.7	3.5	43	71	96	78
15	179	172	100	87	158	148	25	24	126	115	77	94	30	32	2.4	2.4	55	50	84	96
16	196	134	80	64	270	202	23	25	119	87	—	—	—	—	2.9	2.7	69	49	69	92
17	138	128	75	68	149	145	18	12	96	88	62	62	35	34	3.9	3.9	87	80	90	96
18	140	130	95	70	150	122	12	11	110	90	40	37	17	14	1.9	2.1	65	71	48	48
Mean	152	139	74	67	161	154	20	18	100	91	54	56	26	23	2.8	2.8	69	67	74	75
SE		5.4		1.9		4.0		1.6		2.9		2.2		1.6		0.09		4		3
P		<0.05		<0.01		NS		NS		<0.01		NS		NS		NS		NS		NS

* Ten minutes after Innovar injection.

TABLE 3. Changes in Peripheral and Total Pulmonary Resistances after Administration of Innovar

Patient	Systemic Resistance (Units)		Pulmonary Resistance (Units)		Left Ventricular Stroke Work (gm-m)	
	Control	10 Min after Innovar	Control	10 Min after Innovar	Control	10 Min after Innovar
1	36	25	—	—	93	84
2	30	25	—	—	98	94
3	25	32	5	8	54	42
4	33	31	7	5	104	128
5	67	60	39	31	15	18
6	42	40	—	—	134	159
7	45	49	26	24	80	68
8	30	24	6	6	171	122
9	54	42	27	27	38	41
10	35	34	9	7	131	99
11	43	51	—	—	58	50
12	49	52	19	24	76	54
13	17	20	7	7	76	58
14	46	19	—	—	59	78
15	57	48	21	22	65	55
16	43	28	—	—	131	104
17	25	23	12	12	97	89
18	50	43	14	11	85	74
Mean	40.4	35.8*	16.0	15.3	86.9	78.8
SE†		2.0		0.9		4.4

* Significantly different from control mean ($P < 0.05$).
†SE is the standard error of the difference between means of control and 10 minutes after Innovar.

cantly (table 2), with a corresponding decrease in systemic resistance ($P < 0.05$ (table 3). No changes in pulmonary pressures and resistances after Innovar were observed. Pa_{O_2} during breathing of room air decreased from 76 ± 3 mm Hg to 57 mm Hg after injection of the drug, whereas Pa_{CO_2} increased from 35 ± 1 mm Hg to 40 mm Hg, reflected in a decrease in *p*H from 7.50 ± 0.01 to 7.45. All these changes were highly significant ($P < 0.001$) (table 4). Oxygen consumption also decreased significantly, from 142 ml/min/m² to 126 ml/min/m² ($P < 0.01$).

All patients were moderately sedated within two to three minutes after injection; a light sleep, from which they could be easily aroused, had supervened in all by five to six minutes. Respiratory rates slowed. The patients could obey orders but were indifferent to environmental change. None was aware of pain or complained during angiocardiography. Transient ventricular extrasystoles observed during the study were related to manipulation of catheters in cardiac chambers and disappeared upon withdrawal of the catheters.

Discussion

VENTILATION

Alterations in respiratory status were not unexpected, but their severity in some patients with these small doses of Innovar was surprising. The most worrisome finding, decreases in Pa_{O_2} in all patients, to values as low as 38 mm Hg, has an important clinical implication. The need for increased inspiratory oxygen in this situation is clear. The elevation of Pa_{CO_2}, while less worrisome, seems to indicate a definite decrease in alveolar ventilation. The modest increase in P_{CO_2} suggests that assisted ventilation may be necessary in certain instances when the effects of an elevated Pa_{CO_2} on already-altered hemodynamics would be inadvisable. We presume that the respiratory depression results primarily from the effects of the fentanyl portion of Innovar on the respiratory center.[7]

TABLE 4. Changes in Blood Gases and Oxygen Consumption after Administration of Innovar

Patient	Pa_{O_2} (mm Hg)		Pa_{CO_2} (mm Hg)		pH		O_2 Consumption (ml/min/m²)	
	Control	10 Min after Innovar	Control	10 Min after Innovar	Control	10 Min after Innovar	Control	10 Min after Innovar
1	78	66	38	41	7.47	7.43	—	—
2	71	54	33	40	7.48	7.38	—	—
3	90	56	30	35	7.60	7.52	135	106
4	73	60	35	34	7.47	7.48	—	—
5	70	50	43	50	7.54	7.47	154	132
6	71	66	39	41	7.45	7.42	—	—
7	84	66	34	40	7.51	7.44	157	144
8	71	60	33	35	7.47	7.44	148	140
9	54	38	29	37	7.56	7.48	153	137
10	85	53	23	30	7.66	7.56	172	140
11	85	69	33	40	7.46	7.36	132	111
12	65	44	34	39	7.52	7.46	121	119
13	94	81	29	40	7.51	7.46	—	—
14	60	56	40	43	7.46	7.44	—	—
15	97	41	35	44	7.47	7.41	—	—
16	68	43	32	41	7.50	7.40	—	—
17	78	59	36	43	7.51	7.44	—	—
18	77	55	42	47	7.45	7.44	108	101
Mean	76	57*	35	40*	7.50	7.45*	142	126†
SE‡		3		1		0.01		3.4

Significantly different from control mean: * $P < 0.001$; † $P < 0.01$.
‡ SE is the standard error of the difference between means of control and 10 minutes after Innovar.

HEMODYNAMICS

The significant decreases in systemic systolic, diastolic, and mean pressures were due solely to decreases in systemic resistance: cardiac indices remained unchanged.

Yelnosky and co-workers [8] have related the decrease in peripheral resistance seen with the droperidol portion of Innovar to adrenergic blockade and interference with epinephrine at alpha receptor sites. That is, droperidol would be expected to antagonize the peripheral vasoconstrictor effect without affecting the positive inotropic or chronotropic actions of epinephrine.

Determinants of myocardial inotropic activity are difficult to evaluate and understand even in *in vitro* experiments. An evaluation of this aspect of Innovar action in this study can be, at best, only a crude guess. Some clues are available, in that cardiac index, stroke volume, and stroke work all were unchanged. A disproportionate increase of left ventricular end-diastolic pressure in relation to stroke work may reflect a negative inotropic effect.[9] However, there was no consistent change in LVEDP. There is certainly no suggestion in these data of a reproducible pattern of inotropic effects following Innovar. Additionally, heart rate did not change and, therefore, chronotropic activity was not altered.

It is possible that depressant effects on the cardiovascular system were masked by the stimulating effects of hypoxemia and hypercarbia. It has been shown that in intact man [10, 11] increased activity of the sympathetic nervous system increases blood pressure, cardiac output and rate, stroke volume, and contractility. A comparison of the four patients who had Pa_{O_2} values below 44 mm Hg with the five patients who had Pa_{O_2}'s above 65 mm Hg reveals no trend in the hemodynamic changes that would support the idea of a significant sympathetic response to the hypoxemia.

The hypotension seen in this study deserves further comment. It is apparent that in each

of the three patients with the greatest decreases in mean arterial pressure (from 26 to 32 mm Hg) aortic stenosis was the predominant lesion. The diastolic pressures after Innovar in these three ranged from 42 to 64 mm Hg, and 42 mm Hg was the lowest diastolic pressure found in the study. Low diastolic pressures should be considered hazardous to adequate coronary perfusion, particularly in patients with aortic stenosis and associated myocardial hypertrophy who have abnormally great oxygen requirements.

The peripheral dilatation seen with Innovar may have a positive effect. The four patients with the greatest peripheral resistance values prior to the administration of Innovar (Patients 5, 9, 15, and 18), all of whom had peripheral resistance values of 50 units or more, had mitral-valve lesions. Diastolic pressures decreased modestly, but not to the levels seen in patients with aortic stenosis, while the cardiac indices either improved or remained the same. This observation may support the use of adrenergic blocking agents such as phenoxybenzamine[12] for patients who have certain cardiac conditions and high peripheral vascular resistances during and after cardiac surgery.

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Pediatrics

CARDIAC CATHETERIZATION Cardiac catheterization was performed in 45 children 2 to 6 years of age using a combination of basal sedation and axillary plexus block. Basal sedation was accomplished with droperidol, 0.3 to 0.6 mg/kg, and Omnopon, 0.7 mg/kg, administered 90 minutes prior to the axillary block. The block was accomplished using 1.25 to 1.5 mg/kg of bupivacaine (0.25 containing 1/400,000 epinephrine). A sleep dose of thiopental was given to the occasional patient who was still awake and restless at the start of catheterization. No patient required further sedation for the procedure, which often included selective angiocardiography. The technique provided an immobile arm with pronounced vasodilation which permitted the use of larger catheters, made blood sampling easier and provided undamped pressure records. The absence of ventilatory depression was confirmed by oxygen saturation values within the normal range in those patients who did not have cyanotic heart disease or right-to-left shunts. (*Ross, D. M., and Williams, D. O.: Combined Axillary Plexus Block and Basal Sedation for Cardiac Catheterization in Young Children, Brit. Heart J. 32: 195 (March) 1970.*)