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THE CIRCULATORY EFFECTS OF BRADYKININ IN NORMAL SUBJECTS AND PATIENTS WITH CHRONIC BRONCHITIS

BY

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It has been established that bradykinin is a powerful vasodilator in the forearm and hand of man (Fox, Goldsmith, Kidd & Lewis, 1961). The effect upon cardiac output in man or in the conscious animal had not been reported at the time when a preliminary report was made of the present studies (Bishop, Harris & Segel, 1962). Similarly there was no information as to the response of the intact pulmonary circulation, although Waaler (1961) had reported that single injections produced a fall in pulmonary vascular resistance in the perfused dog lung. Since this suggested the possibility of a pulmonary vasodilator action in man, it was decided also to investigate the effects of bradykinin in patients with pulmonary hypertension due to chronic bronchitis. Studies of this type were possible because of the availability of synthetic bradykinin (Boissonas, Guttman & Jaquenoud, 1960).

METHODS

Subjects and patients studied

Eight subjects with a normal cardiovascular and respiratory system and seven patients with chronic bronchitis have been studied in the recumbent position. Details of their physical characteristics are given in Tables 1 and 3.

The normal subjects were investigated by cardiac catheterization because of the presence of either a systolic murmur or a complaint of breathlessness, for neither of which was any organic cause subsequently found. The diagnosis of chronic bronchitis was based upon a history of long standing productive cough and shortness of breath on exertion. Obstructive airways disease was confirmed by measurement of the forced expiratory volume at 1 sec, which was considerably reduced in all patients, ranging from 0.56 to 1.37 l. with a mean of 0.84 l. These observed volumes were from 19 to 37% (mean 29%) of the predicted normal values.

Technical methods

A double-lumen catheter was advanced from a cubital vein into the lung so that its tip was wedged into a peripheral artery while the proximal orifice lay in the pulmonary arterial trunk or one of its main branches. In all but four of the studies a double-lumen catheter was also inserted from the opposite arm into the right atrium. Bradykinin was delivered into the superior vena cava through the proximal orifice of the right atrial catheter by a constant infusion pump, and in four patients it was delivered into a cubital vein. The dose of bradykinin ranged from 0.3 to 1.0 μg/kg/min, in a volume of 2.0 ml./min.

It was subsequently discovered that the bradykinin solution contained chlorbutol, 5 mg/ml., as a preservative, so that with the larger doses of bradykinin chlorbutol was being infused as well at a rate of about 3.5 mg/min. In a separate experiment chlorbutol alone was infused at a similar rate, but no significant alterations were observed in heart rate or systemic blood pressure.

Brachial arterial pressure was measured through an indwelling needle. The intravascular pressures were measured by capacitance manometers and recorded by a multi-channel direct-writing instrument. The zero reference level for pressures was 10 cm above the plane of the catheterization table. Mean pressures were determined by planimetry and all pressures were averaged over at least three respiratory cycles.

The cardiac output was measured by the direct Fick method. Expired gas was collected in a Tissot spirometer during a period of 2 min during which time two samples each of arterial and mixed venous blood were taken for the spectrophotometric determination of the oxyhaemoglobin percentage. The blood oxygen capacity was determined photometrically, a sample being taken during each estimation of the cardiac output. Expired gas was analysed in a Scholander apparatus.

Procedure

Each subject and patient was studied at rest without sedation 6 hr after a light meal. The design of the study will be evident from Fig. 1, each study consisting of three measurement periods: a preliminary period of 10 min, a period of 15 min during which bradykinin was infused and a further period of 15 min after the infusion had been stopped. The cardiac output was measured once before the infusion, twice during the infusion and twice after the infusion ceased.

Intravascular pressures were measured immediately before and after each measurement of cardiac output. In one normal subject (W.P.) the infusion was stopped after 8 min because the brachial arterial pressure fell considerably.

The effects of bradykinin before and after the administration of pronethalol were studied in two normal subjects (F.P. and B.W.). Pronethalol (1.25 mg/kg) was delivered into the pulmonary artery during 12 min by a constant infusion pump, and the second infusion of bradykinin commenced 15 min later.

RESULTS

The infusions caused symptoms similar to those previously described, notably flushing and sensations of heat. These symptoms were greatest from 5 to 8 min after starting the infusion, and thereafter they diminished. Wheezing was noted in two of the patients with chronic bronchitis (M.N. & G.W.), but this did not occur in any of the normal subjects.

The results in the normal subjects are given in Tables 1 and 2 and those for the patients with chronic bronchitis in Table 3. The figures for heart rate and intravascular pressures represent the average of two measurements made immediately before and after each measurement of cardiac output.

A representative study in a normal subject (G.H.) is shown in Fig. 1. The effects of bradykinin on the circulation before and after pronethalol are shown in Fig. 2, which gives the average values for two subjects. The average values for cardiac output, heart rate and intravascular pressures before, during and after the infusion of bradykinin in the seven patients with chronic bronchitis are shown in Fig. 3.

Effects on systemic circulation

The effects of bradykinin on cardiac output, heart rate and brachial arterial pressure were similar in the normal subjects and patients. In each instance there was an increase in cardiac output and heart rate and a fall in brachial arterial pressure. In the normal

TABLE 1

EFFECTS OF THE INFUSION OF BRADYKININ ON CARDIAC OUTPUT AND RELATED MEASUREMENTS AND INTRAVASCULAR PRESSURES IN NORMAL SUBJECTS AT REST

M = male; F = female; B.S.A.= body surface area; S = systolic; D = diastolic; M = mean. Oxygen saturation refers to systemic arterial blood

Subject			Dose of bradykinin				Blood		Heart			Pressure (mm Hg)									Pulmonary vascular resistance
												Brachial artery			Pulmonary artery			Pulmonary wedge	Right atrium		
Sex, weight (kg)	Age, B.S.A. (m^2)		Dose of bradykinin (μg/kg/min)	Period	Oxygen uptake (ml./min/m^2)	Pulmonary ventilation (l./min/m^2)	Oxygen capacity (ml./100 ml.)	Oxygen saturation (%)	Output (l./min/m^2)	Rate (per min)	Stroke volume (ml./m^2)	S	D	M	S	D	M	M	M		(dyne sec cm^{-5})
D.J.			0·3	Before	118	7·1	16·1	99·3	3·5	73	48	147	80	111	25	11	17	12	6		82
				During	124	7·1	16·7	99·4	4·1	82	50	132	73	103	30	14	21	12	7		112
F	50			During	139	7·2	16·6	99·4	3·9	80	49	131	78	108	27	13	19	11	7		105
55	1·57			After	129	7·4	16·4	99·1	2·8	68	41	155	80	114	25	11	17	10	7		127
				After	130	7·6	15·9	99·3	2·7	66	41	155	78	112	25	11	17	11	7		112
V.B.			0·3	Before	140	3·8	17·3	97·7	5·3	105	50	181	96	124	29	13	22	13	6		82
				During	146	4·0	17·3	97·4	7·1	130	55	149	83	113	30	15	23	13	4		67
F	22			During	144	4·1	17·4	97·4	6·6	131	50	148	84	114	28	13	21	10	2		80
60	1·67			After	131	4·2	16·7	98·3	4·9	112	44	162	96	122	22	9	16	7	3		88
				After	132	3·6	16·1	97·3	5·9	104	57	156	93	119	25	12	20	11	4		74
C.W.			0·4	Before	149	3·3	18·6	93·1	6·8	82	83	159	92	122	33	13	21	13	7		57
				During	154	4·3	18·7	93·2	8·9	90	99	163	83	118	34	16	25	14	8		55
M	44			During	154	5·0	18·6	93·8	7·1	90	79	166	89	124	32	15	24	14	8		62
74	1·81			After	145	5·7	18·3	93·9	5·4	86	63	182	100	131	27	11	19	14	8		41
				After	149	5·6	18·2	93·7	5·7	88	65	169	95	125	25	11	15	13	8		24
P.W.			0·5	Before	132	3·5	17·7	98·8	3·5	82	43	142	81	110	30	16	22	11	8		152
				During	118	3·3	17·7	98·8	4·1	103	40	136	78	103	28	13	20	7	5		135
F	26			During	136	3·5	17·3	98·4	4·7	108	44	135	77	104	27	11	19	6	6		135
59	1·65			After	142	4·8	16·9	99·7	3·5	89	39	130	79	98	22	8	16	7	5		124
				After	158	5·1	16·7	98·8	4·1	88	47	130	78	99	25	10	18	9	4		106
F.P.			0·8	Before	135	3·9	15·4	94·8	3·5	88	40	146	90	115	27	11	19	9	7		129
				During	131	4·2	17·1	95·3	4·9	107	46	137	77	100	32	15	23	6	5		158
F	29			During	124	3·7	17·1	94·8	3·9	100	39	140	82	105	26	9	17	7	5		114
70	1·76			After	124	3·5	16·7	96·9	2·5	82	30	146	93	116	19	9	14	7	4		127
				After	127	3·8	15·7	96·7	2·7	82	30	140	95	116	22	11	16	7	6		153
B.W.			0·8	Before	116	3·2	15·4	97·5	3·5	78	45	140	80	114	31	12	20	11	7		124
				During	127	4·0	15·9	96·3	5·3	100	53	124	68	96	35	16	25	11	8		127
F	36			During	128	3·9	15·9	97·0	5·2	97	53	135	78	107	32	14	22	10	8		113
60	1·65			After	131	3·2	15·7	97·8	3·4	75	48	140	81	116	27	12	20	9	7		157
				After	119	3·7	15·7	95·7	3·7	78	48	138	79	114	29	12	20	9	7		144

Table 1 *contd.*

Subject		Dose of brady-kinin			Blood		Heart			Pressure (mm Hg)								Pulmonary vascular resistance
Sex, weight (kg)	Age, B.S.A. (m^2)	(μg/kg/min)	Period	Oxygen uptake (ml./min/m^2)	Pulmonary ventilation (l./min/m^2)	Oxygen capacity (ml./100 ml.)	Oxygen saturation (%)	Output (l./min/m^2)	Rate (per min)	Stroke volume (ml./m^2)	Brachial artery S	Brachial artery D	Brachial artery M	Pulmonary artery S	Pulmonary artery D	Pulmonary artery M	Pulmonary wedge M	Right atrium M	(dyne sec cm^{-5})
G.H.		1·0	Before	135	4·5	16·6	96·2	3·7	83	45	158	84	114	30	16	22	13	8	126
			During	145	6·0	17·8	96·0	6·1	102	60	120	61	88	29	15	21	15	8	50
F	40		During	138	5·4	18·0	96·3	5·3	109	49	144	79	109	29	14	20	13	7	67
57·5	1·57		After	134	4·5	17·5	95·1	3·6	84	43	159	86	117	30	16	22	16	9	86
			After	135	5·3	17·1	96·0	3·5	80	44	158	83	118	31	17	23	13	8	146
W.P.		1·0	Before	127	3·7	17·7	99·6	4·3	88	49	151	72	102	23	12	17	9	6	93
			During	125	4·1	19·0	99·6	6·9	115	60	112	52	72	21	8	14	9	5	36
F	32		During	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
61·8	1·61		After	120	3·2	18·3	99·3	3·5	88	40	138	70	96	18	5	12	11	5	84
			After	128	3·3	17·9	97·7	3·8	95	40	138	74	99	20	7	14	10	4	77
			t			2·78	1·79	5·89		3·62						0·78	0·80		
			P			<0·05	<0·1	<0·001		<0·01						<0·1	<0·1		

TABLE 2

EFFECTS OF THE INFUSION OF BRADYKININ ON CARDIAC OUTPUT AND RELATED MEASUREMENTS AND INTRAVASCULAR PRESSURES IN TWO NORMAL SUBJECTS (F.P. AND B.W.) AFTER PRONETHALOL

Abbreviations as for Table 1

Subject	Dose of bradykinin (μg/kg/min)	Period	Oxygen uptake (ml./min/m²)	Pulmonary ventilation (l./min/m²)	Blood: Oxygen capacity (ml./100 ml.)	Blood: Oxygen saturation (%)	Heart: Output (l./min/m²)	Heart: Rate (per min)	Heart: Stroke volume (ml./m²)	Pressure (mm Hg): Brachial artery S	Brachial artery D	Brachial artery M	Pulmonary artery S	Pulmonary artery D	Pulmonary artery M	Pulmonary wedge M	Right atrium M	Pulmonary vascular resistance (dyne sec cm⁻⁵)
F.P.	0·8	Before	126	3·8	15·5	99·1	2·7	80	34	145	93	114	24	12	19	8	6	187
		During	130	3·5	16·3	96·3	4·5	89	51	133	69	91	28	13	21	6	5	152
		During	130	3·5	16·5	98·2	3·2	83	39	138	77	100	25	12	18	7	6	157
		After	127	3·5	16·1	98·7	2·5	81	31	143	90	113	25	12	18	9	6	160
		After	125	3·6	15·4	96·9	2·5	80	31	141	91	113	25	10	17	9	6	142
B.W.	0·8	Before	131	3·2	15·3	98·0	3·4	75	46	137	79	114	27	12	19	11	7	114
		During	145	4·0	15·2	97·2	5·0	74	68	118	63	94	28	14	21	11	9	98
		During	147	3·8	15·3	98·6	4·1	66	62	122	68	99	27	12	20	10	9	120
		After	124	3·8	15·3	98·6	2·6	66	40	133	79	110	24	11	17	10	8	130
		After	119	3·7	15·2	97·1	3·7	76	46	128	77	107	25	12	18	10	7	105

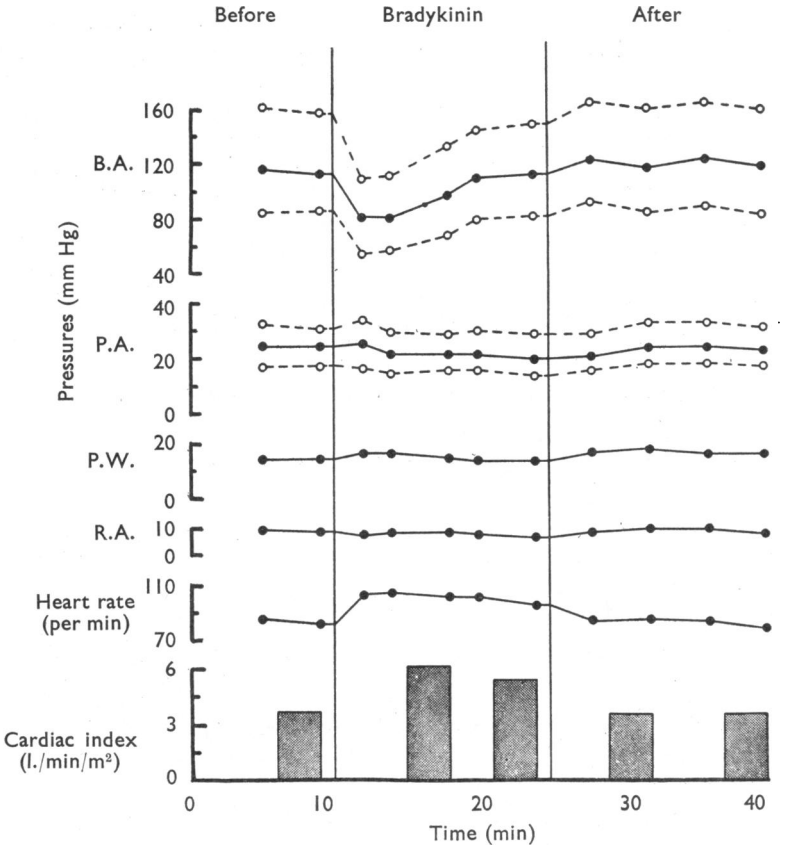

Fig. 1. The effects of the infusion of bradykinin (1 μg/kg/min) on cardiac output, heart rate and intravascular pressures in subject G.H. B.A.=brachial arterial pressure; P.A.=pulmonary arterial pressure; P.W.=pulmonary wedge pressure, R.A.=right atrial pressure. All pressures in mm Hg.

subjects the rise in cardiac output was proportionately greater than the increase in heart rate, due to a significant increase in stroke volume. These changes were most pronounced in the first half of the infusion period when flushing of the skin was greatest. In general the changes in cardiac output, heart rate and arterial pressure in the normal subjects tended to be greatest with the larger doses of bradykinin. The mean rise in cardiac output, although significant, was not as large in the patients with chronic bronchitis as in the normal subjects; there was no increase in one patient (M.N.) and little change in two others (A.H. and W.N.). There was little change in stroke volume in any patient.

When the rise in heart rate during the infusion of bradykinin was prevented or greatly diminished by prior administration of the sympathetic β-receptor blocking agent pronethalol, the cardiac output still rose and the stroke volume increased to an even greater extent than before.

The oxygen uptake, ventilation, respiratory exchange ratio and arterial oxygen saturation remained unaffected by the infusion of bradykinin into the normal subjects. In the

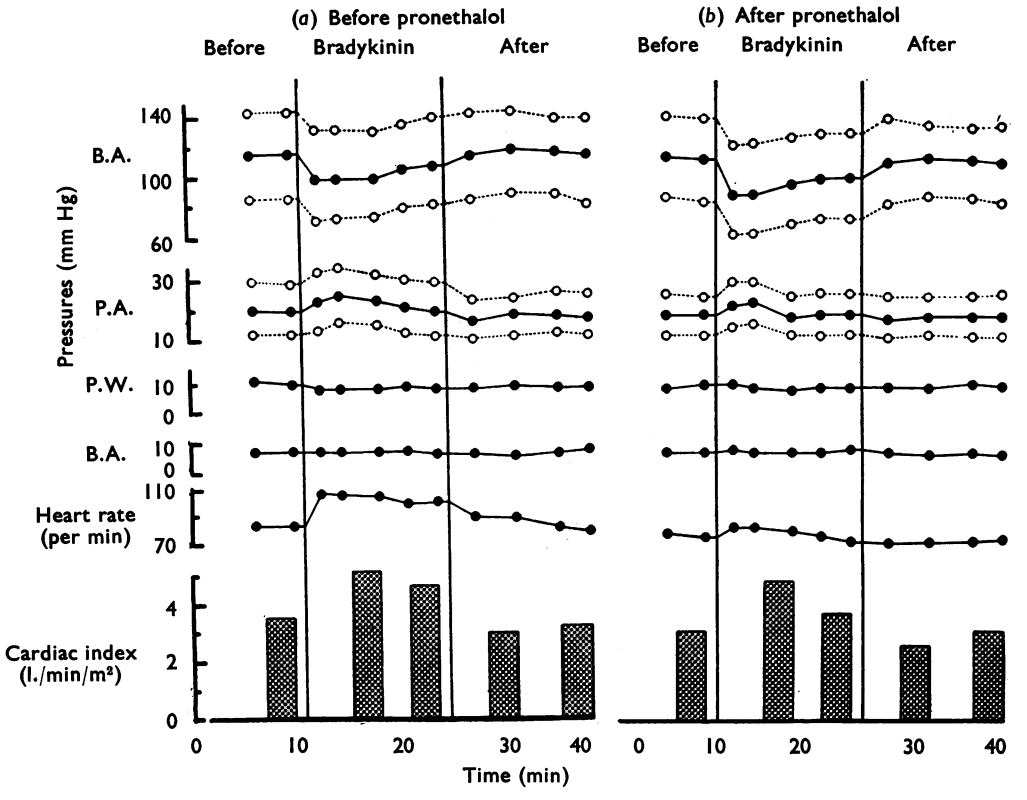

Fig. 2. The effects of the infusion of bradykinin (0.8 μg/kg/min) on cardiac output, heart rate and intravascular pressures before and after pronethalol (1.25 mg/kg). Average values for two subjects (F.P. and B.W.). B.A. = brachial arterial pressure, P.A. = pulmonary arterial pressure, P.W. = pulmonary wedge pressure, R.A. = right atrial pressure All pressures in mm Hg.

patients with chronic bronchitis both oxygen uptake and ventilation showed small but insignificant increases, and the respiratory exchange ratio remained unchanged. In one patient only (M.R.) was there a marked fall in arterial oxygen saturation associated with a reduction in ventilation. Alveolar oxygen tension in this patient fell from 83 to 64 mm Hg and arterial oxygen tension fell from 50 to 31 mm Hg.

The blood oxygen capacity increased significantly during the infusion period in both the normal subjects and patients and the rise was greatest with the higher doses of bradykinin. The mean increase in subjects receiving 0.8 μg/min or more was 1.5 ml./100 ml. while in subjects receiving a smaller dose it was 0.4 ml./100 ml.

During the second half of the infusion period the changes in cardiac output, heart rate and brachial arterial pressure were less striking than initially and it appeared that the effects of bradykinin were diminishing.

Effects on the pulmonary circulation

Normal subjects. With doses of bradykinin ranging from 0.3 to 0.8 μg/kg/min there was a small rise in the pulmonary arterial mean pressure in all but one of the subjects.

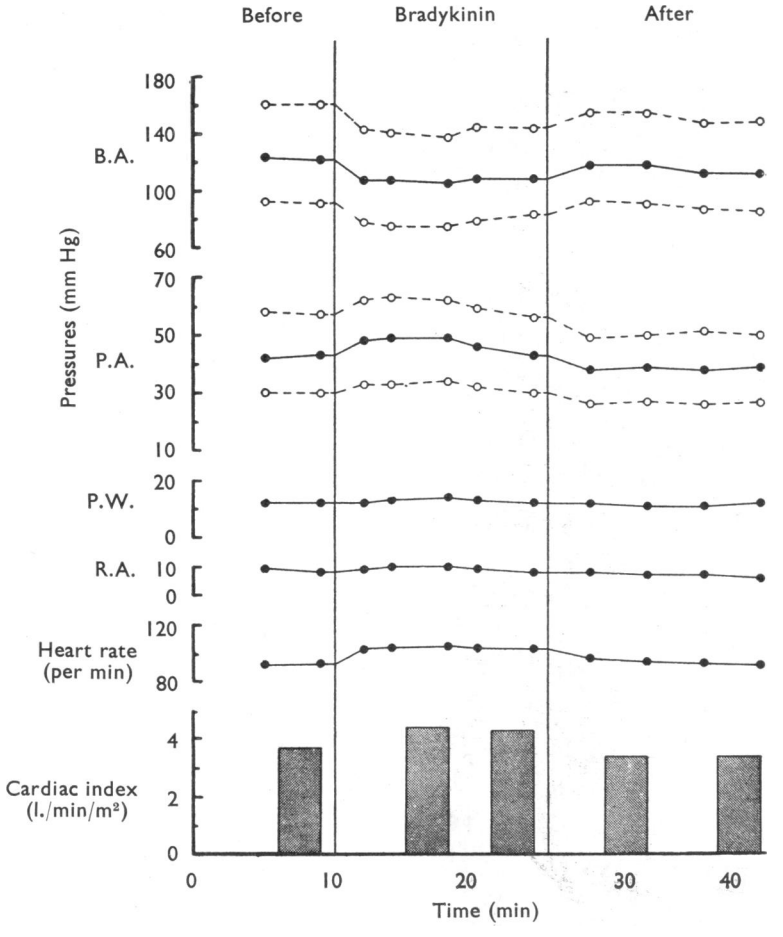

Fig. 3. The effects of the infusion of bradykinin on cardiac output, heart rate and intravascular pressures in patients with chronic bronchitis. Average values for seven patients. B.A. = brachial arterial pressure, P.A. = pulmonary arterial pressure, P.W. = pulmonary wedge pressure, R.A. = right atrial pressure. All pressures in mm Hg.

Pulmonary wedge pressure remained unchanged and consequently there was a greater fall in pressure across the lung. However the increase in pulmonary blood flow was proportionate to the increased fall in pressure, so that the calculated pulmonary vascular resistance remained unaltered during the infusion period. This type of response is shown in Fig. 2.

When the dose of bradykinin was larger the pulmonary arterial mean pressure fell slightly, but the pulmonary wedge pressure did not change and the drop in pressure across the lung decreased (Fig. 1). In these two subjects there was a large increase in cardiac output and the calculated pulmonary vascular resistance decreased.

Right atrial pressure remained unaltered during the infusion period. Previous administration of pronethalol had little or no effect on the changes produced by bradykinin in the pulmonary circulation (Fig. 2).

TABLE 3

EFFECTS OF THE INFUSION OF BRADYKININ ON CARDIAC OUTPUT AND RELATED MEASUREMENTS AND INTRAVASCULAR PRESSURES IN PATIENTS WITH CHRONIC BRONCHITIS

Abbreviations as for Table 1

Patient		Dose of bradykinin									Pressure (mm Hg)										
					Pulmonary ventilation	Blood		Heart			Brachial artery			Pulmonary artery			Pulmonary wedge	Right atrium	Pulmonary vascular resistance
Sex, weight (kg)	Age, B.S.A. (m^2)	(μg/kg/min)	Period	Oxygen uptake (ml./min/m^2)	(l./min/m^2)	Oxygen capacity (ml./100 ml.)	Oxygen saturation (%)	Output (l./min/m^2)	Rate (per min)	Stroke volume (ml./m^2)	S	D	M	S	D	M	M	M	(dyne sec cm^{-5})
G.W.		0·3	Before	126	3·9	20·8	93·2	2·2	89	25	144	90	115	39	23	30	9		426
			During	116	3·7	21·4	93·8	2·5	92	27	136	85	106	45	27	36	10		473
M	46		During	124	3·8	21·3	94·1	2·5	95	25	142	89	111	41	26	33	9		436
62·5	1·74		After	129	4·0	21·5	94·0	2·1	92	23	146	94	116	38	24	30	10		432
			After	129	3·9	21·4	94·8	2·1	93	23	139	86	110	37	23	29	9		432
A.H.		0·4	Before	158	5·3	23·3	86·4	3·0	74	41	195	94	139	63	26	43	7		554
			During	174	5·6	23·6	85·0	3·8	87	44	172	84	119	72	32	51	6		545
M	41		During	168	5·4	23·6	83·2	3·6	85	42	180	90	126	68	30	47	7		524
62·5	1·74		After	177	5·6	23·6	82·8	2·9	74	39	180	103	136	58	24	42	7		560
			After	148	5·0	22·7	83·4	2·8	73	42	177	97	128	56	24	39	7		533
M.N.		0·5	Before	169	5·2	21·6	62·8	4·0	97	41	116	62	87	77	42	58	16		473
			During	180	6·0	22·3	65·8	3·9	100	39	92	47	76	61	37	51	15		417
F	61		During	164	6·5	22·0	63·8	4·0	103	39	105	61	82	60	35	49	15		377
78	1·78		After	179	6·6	21·9	63·2	3·5	98	36	121	64	89	63	35	50	14		457
			After	181	6·3	21·8	67·6	3·8	96	39	109	59	80	63	35	51	17		406
M.R.		0·7	Before	166	5·0	18·6	83·9	3·6	104	35	165	106	135	79	49	61	20	13	556
			During	162	4·2	18·5	65·4	4·6	133	35	140	87	115	90	58	74	25	16	516
F	45		During	206	4·9	19·3	69·8	5·3	136	39	140	87	115	90	58	74	24	15	455
65	1·65		After	168	5·0	19·2	85·0	3·9	119	33	142	94	120	72	40	55	20	11	438
			After	157	4·7	19·6	85·6	3·4	117	29	146	98	123	75	44	57	19	11	553
A.F.		0·8	Before	161	8·5	21·9	80·9	3·4	85	40	195	103	147	35	17	25	13	8	204
			During	176	9·0	24·7	79·6	4·1	97	42	160	77	113	39	19	29	15	7	193
M	59		During	177	8·8	24·5	78·1	4·0	97	41	184	96	129	35	17	26	12	5	200
44·5	1·41		After	165	8·5	23·7	78·0	3·6	92	39	185	100	132	32	17	33	13	5	157
			After	161	8·5	23·1	79·5	3·5	84	42	165	87	117	29	14	22	9	5	210

Table 3 *contd.*

Patient		Dose of brady-kinin			Pul-monary ventila-tion	Blood		Heart			Pressure (mm Hg)								Pulmonary vascular resistance
											Brachial artery			Pul-monary artery			Pul-monary wedge	Right atrium	
Sex, weight (kg)	Age, B.S.A. (m^2)	(μg/kg/min)	Period	Oxygen uptake (ml./min/m^2)	(l./min m^2)	Oxygen capacity (ml./100 ml.)	Oxygen saturation (%)	Output (l./min/m^2)	Rate (per min)	Stroke volume (ml./m^2)	S	D	M	S	D	M	M	M	(dyne sec cm^{-5})
J.P.		1·0	Before	155	6·9	19·6	93·7	4·2	99	42	133	81	103	46	22	36	9	6	296
			During	161	8·0	20·6	94·0	4·6	115	40	113	71	90	63	28	49	9	7	400
M	45		During	148	7·8	20·2	93·8	4·0	104	39	103	63	82	54	22	40	10	7	343
58	1·72		After	156	7·3	19·5	92·5	3·2	101	32	124	77	97	42	22	33	10	7	335
			After	155	7·3	19·3	93·5	3·4	101	34	125	78	97	43	22	33	10	5	317
W.N.		1·0	Before	132	3·8	24·0	83·1	3·3	92	37	173	103	131	63	33	46	11		528
			During	155	4·4	25·8	82·6	4·5	102	44	157	77	106	70	37	52	13		427
M	56		During	171	5·0	25·7	85·9	4·0	98	41	158	83	112	55	30	42	11		388
55	1·61		After	129	3·7	25·1	80·8	2·9	92	32	178	110	136	49	26	37	9		487
			After	147	4·1	23·1	80·8	3·2	86	38	162	100	129	49	25	37	11		408
			t	1·84	1·35	2·97	1·18	3·4		1·27						2·39	2·18		1·22
			P	<0·10	<0·10	<0·05	<0·10	<0·02		<0·1						<0·10	<0·10		<0·10

Patients with chronic bronchitis. Before the infusion the pulmonary arterial mean pressure was raised above normal in each of the seven patients and ranged from 25 to 61 mm Hg (mean 43 mm Hg). Cardiac output was in the normal range (Segel, Hudson, Harris & Bishop, 1964) in all but one patient (G.W.), in whom it was reduced. Arterial oxygen saturation was reduced in five patients and was normal in two.

The infusion of bradykinin produced a rise in pulmonary arterial mean pressure in all but one of the patients. In this patient (M.N.) the cardiac output also failed to increase. Pulmonary wedge pressure was not altered by the infusion and consequently the pressure drop across the lungs increased. This increase was proportionate to the increase in pulmonary blood flow, so that the calculated pulmonary vascular resistance did not change significantly during the infusion. Right atrial pressure did not change consistently in the three patients in whom it was measured.

DISCUSSION

The consistent fall in systemic arterial pressure in the normal subjects, in the face of an increase in cardiac output, indicates a reduction in total systemic arterial resistance due to vasodilatation. This fall in arterial pressure was maximal during the early part of the infusion, and thereafter pressure rose as the infusion continued and the final value was often but little below the initial level before the infusion began.

Bradykinin increases capillary permeability (Elliott, Horton & Lewis, 1960) and this, by causing a loss of fluid from the circulation, is presumably the reason for the increased oxygen capacity of the blood which was observed during the infusion, the effect being greater in subjects receiving the larger doses.

Cardiac output invariably increased during the infusion due to an increase in both heart rate and stroke volume. The increased stroke volume was not associated with any rise in ventricular filling pressure, as judged by unaltered right atrial and pulmonary wedge pressures, suggesting that myocardial contractility may have increased. There was, however, a simultaneous fall in systemic arterial pressure ; and the decrease in systolic pressure was of a similar magnitude to the increase in stroke volume, suggesting that the work of the left ventricle did not increase. In order to study this aspect further the infusion was repeated in two subjects after pronethalol had been given to minimize the increase in heart rate during the infusion of bradykinin. Under these circumstances a similar decrease in systemic arterial pressure was now associated with a considerably greater increase in stroke volume. The work of the left ventricle had presumably increased in the face of unaltered ventricular filling pressure, suggesting an increase in myocardial contractility. This is consistent with the observations of Croxatto & Belmar (1961) and Montague, Rosas & Bohr (1963) who found that in animals in which blood pressure had first been reduced by total autonomic blockade, bradykinin produced a rise in systemic blood pressure. This was presumably due to the increase in cardiac output and stroke volume shown by the latter authors, and which could not therefore be explained as a reflex response to a fall in blood pressure.

The secondary rise in arterial pressure as the infusion continued has already been remarked upon, and it was associated with a parallel fall in cardiac output and stroke volume. The cardiac output measured towards the end of the infusion was consistently

less than the first measurement early in the infusion, and stroke volume showed a similar decrease. The response was no different in the two subjects who received pronethalol. The mechanism of these changes is not clear, but they could be associated with the rapid rate of destruction of bradykinin in the blood, the biological half-life being 30 sec or less, according to the experiments of Saameli & Eskes (1962). This would probably explain why Allwood & Lewis (1964) were unable to detect any increase in the bradykinin content of venous blood from an arm in which blood flow had increased many times as a result of intra-arterial infusion of bradykinin. These authors were also unable to detect any increase in the concentration of kininase in the effluent blood during the infusion. They suggested that the increased permeability of the capillaries due to bradykinin might permit bradykinin to escape more readily from the vessels, to be destroyed by tissue kininase. This could explain the present observations, the rate of destruction of bradykinin increasing as the constant infusion continued so that the effective concentration in the blood would decrease. The possibility still remains however that the phenomenon represents true tachyphylaxis, the organs responding less to the same concentration of the active agent.

Feldberg & Lewis (1964) showed that bradykinin releases catechol amines from the adrenal medullae in the anaesthetized cat. If this occurs also in man, it is possible that the level of circulating catechol amines may have risen as the infusion of bradykinin continued in the present experiments and that this may have led to the observed secondary increase in systemic blood pressure.

It seems unlikely that this would also explain the increase in cardiac output, however, since this was greatest early in the infusion and tended to decline as the infusion of bradykinin proceeded, at a time when the increasing concentration of circulating catechol amines would have been expected to cause an increase in cardiac output. The likelihood that the increase in cardiac output was reflexly mediated, and arose from the fall in systemic blood pressure, appeared to be excluded when a similar increase occurred after previous treatment with pronethalol. In both patients the stroke volume achieved during the infusion of bradykinin after pronethalol was greater than before, with the same right atrial and pulmonary wedge pressures, and similar systemic arterial pressure. These observations make it unlikely that an increase in circulating catechol amines led to the raised cardiac output and suggest that bradykinin had a direct stimulating effect upon the myocardium.

The effects upon the pulmonary circulation were not pronounced, and appeared to be related to the dose administered. Five of the six normal subjects who received smaller doses of bradykinin showed small increases in pulmonary arterial pressure consistent with the increased pulmonary blood flow. There was a small reduction of pulmonary arterial pressure in the two subjects who had the largest dose, and in these subjects only was there a possibly significant reduction in pulmonary vascular resistance. Alterations in pulmonary wedge and right atrial pressures were small and insignificant. Bradykinin possibly leads to pulmonary vasodilatation in the larger doses, but has no direct effect upon the pulmonary resistance vessels in the smaller doses which are still sufficient to cause systemic vasodilatation.

The effects of bradykinin infusion in the patients with chronic bronchitis and pulmonary hypertension were, in most respects, qualitatively the same as in normal subjects. The

reason for the smaller than normal increase in cardiac output and stroke volume is not certain, but possibly myocardial function was impaired, this being associated with right ventricular hypertrophy due to pulmonary hypertension. By contrast the fall in systemic blood pressure was the same in the patients as in the normal subjects. Pulmonary arterial pressure increased considerably in those patients who did have a rise in cardiac output but the changes in pulmonary vascular resistance were inconsistent and never large.

Bradykinin presumably caused narrowing of the airways in some of the patients with chronic bronchitis. Although bradykinin causes bronchoconstriction in the guinea-pig (Elliott *et al.*, 1960), this feature has not been previously reported in man. The effect in man may still be a slight one, however, since the patients concerned were suffering from severe obstructive airways disease and were therefore especially susceptible to slight further bronchoconstriction. The present observations do not suggest that infusions of bradykinin have any place in the treatment of such patients.

SUMMARY

1. Bradykinin (0.3 to 1.0 μg/kg/min) was infused intravenously for 15 min into eight normal subjects and seven patients with chronic bronchitis. Cardiac output was measured by the direct Fick method and intravascular pressures were directly recorded.

2. Brachial arterial pressure fell, while heart rate, stroke volume and cardiac output increased. All of these changes were greatest during the first half of the infusion, and diminished thereafter.

3. After previous administration of pronethalol, bradykinin caused only a small increase in heart rate, but stroke volume still increased, suggesting that bradykinin has a direct stimulant effect upon the myocardium.

4. The smaller doses of bradykinin caused small increases in pulmonary arterial and pulmonary wedge pressures, but larger doses sometimes resulted in a fall in pulmonary arterial pressure. While small doses have no direct effect upon the pulmonary circulation, larger doses may cause pulmonary vasodilatation.

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