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CARDIOPULMONARY CONSEQUENCES OF PYROGEN-INDUCED HYPERPYREXIA IN MAN *

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The physiologic consequences of hyperpyrexia attracted considerable interest when artificially-induced fever was a popular therapeutic maneuver (1–10). Although induced hyperpyrexia has lapsed from therapeutic favor, the effects of body temperature elevation in response to infection, environmental factors, or pyrogenic drugs remain a source of concern, especially in patients with cardiac or pulmonary dysfunction.

Prior investigations have indicated that fever, whether induced by external heating or pyrogen injection, is accompanied by significant cardiac and peripheral hemodynamic alterations in both animals and man (1–4, 10, 11). However, data concerning respiratory gas exchange, pulmonary hemodynamics, and arterial blood gas composition in hyperpyrexia are rather fragmentary and inconclusive (7–9, 12–17).

The purpose of this study was to evaluate simultaneously the changes in body temperature, pulmonary and systemic hemodynamics, respiratory gas exchange, and arterial blood gas composition that occur in normal subjects after the intravenous injection of a pyrogenic lipopolysaccharide extract of gram-negative bacilli. Since prior studies in man have not included cardiac catheterization and detailed measurement of respiratory function, it was felt that an investigation using the techniques now available would shed further light upon the cardiopulmonary consequences of the pyrogenic reaction in man.

MATERIALS AND METHODS

Ten male subjects ranging from 33 to 74 years of age (mean 45.6) were studied. All were free of cardiac and pulmonary disease by clinical and routine laboratory criteria. All subjects were studied in the morning after an overnight fast. No sedation was employed prior to or during the test period.

The pulmonary artery was catheterized under fluoroscopic guidance via the brachial vein, and a Cournand needle was placed percutaneously in the contralateral brachial artery. Pressure measurements were carried out with Statham strain gauges and recorded with a multichannel Electronics-for-Medicine photographic unit. Mean pressures were determined by electronic integration. Cardiac output was determined by the Fick principle. Expired air was collected for 5 minutes in a Douglas bag with blood samples obtained simultaneously from brachial artery and pulmonary artery at the midpoint of the air collection. Expired air samples were analyzed for oxygen and carbon dioxide in the Scholander apparatus (18). Duplicate checks within 0.02% were required. Blood oxygen content and capacity were determined in the Haldane apparatus (15). Duplicate checks within 0.2 vol % were required. Blood carbon dioxide content was determined in the Van Slyke apparatus with duplicate checks within 0.2 vol % required. Determination of blood pH was carried out anaerobically by using a Cambridge pH meter and a capillary glass electrode with water jacket. Temperature of the water perfusing the jacket during pH measurement was brought to within $\pm 0.1°$ C of the body temperature present at the time of sample withdrawal by a Haake temperature-pump system. Rectal temperature was continuously monitored by an indwelling rectal thermocouple and a Yellow Springs Telethermometer unit. Respiratory rate was directly counted. Cardiac rate was determined by standard limb lead electrocardiograms. Vascular resistances were calculated with the following formulas:

$$\textit{total pulmonary resistance} = \frac{PAm\ (mm\ Hg) \times 80}{Q\ (L/min)}$$

and

$$\textit{total systemic resistance} = \frac{BAm\ (mm\ Hg) \times 80}{Q\ (L/min)}.$$

Arterial P_{CO_2} was calculated from the Henderson-Hasselbalch equation, with a pK_1' and solubility factor corrected for body temperature (7, 15). P_{AO_2} was calculated from the alveolar air equation (15).

Five studies were carried out in each patient. Study 1 (control) was carried out fifteen minutes after introduction of the cardiac catheter and brachial artery needle, but prior to pyrogen injection. After this study, 0.45 μg

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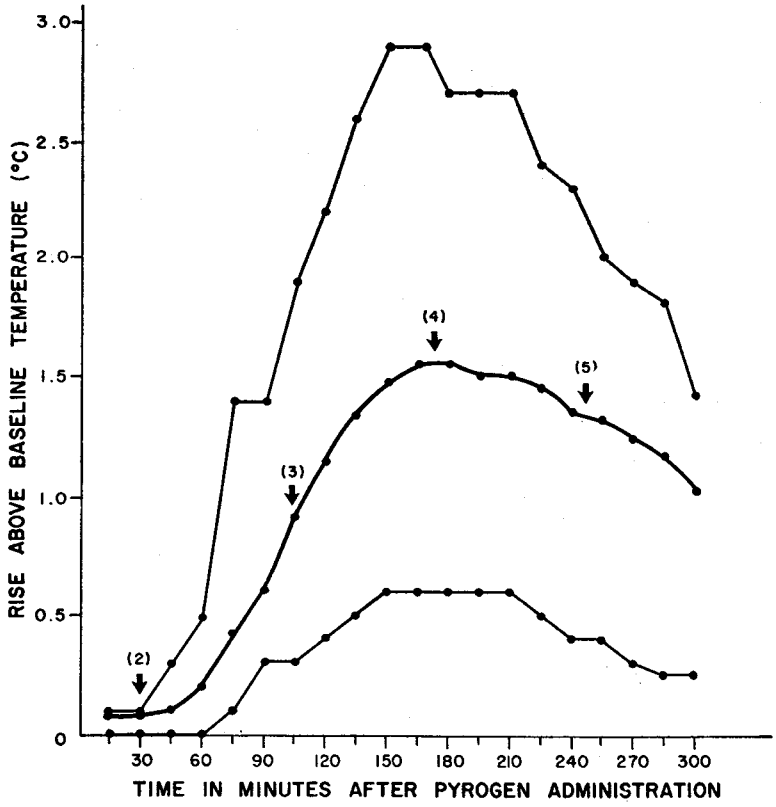

FIG. 1. TEMPERATURE RESPONSE TO PYROGEN INJECTION. Middle curve represents group mean; upper and lower curves indicate range. Arrows indicate time of prodrome (2), chill (3), flush (4), and defervescent (5) phase studies.

of a pyrogenic lipopolysaccharide extract of gram-negative bacilli[1] was administered intravenously. Study 2 (prodrome phase) was carried out approximately 30 minutes after pyrogen injection, at which time no patient had a temperature elevation above 0.1° C. Study 3 (chill phase) was begun 30 minutes after an upswing of the temperature curve was established, except in five patients who had frank chills at this time. In these subjects, study 3 was delayed for at least 15 minutes after cessation of the chill. Study 4 (flush phase) was carried out after rectal temperature had reached and stabilized at its peak level for at least 15 minutes. Study 5 (defervescent phase) was carried out approximately 60 minutes after the temperature had begun to decline from its peak value.

RESULTS

Data obtained during the prodrome, chill, flush, and defervescent phases were compared with data obtained during the control period. In addition, data from the five patients who experienced chills were compared with those from the five subjects without chills. Differences between control and subsequent study periods and between the chill and no chill groups, with "p value" of 0.05 or less, are referred to below as "significant," although statement of statistical significance does not imply physiologic significance. Data derived during the chill and defervescent phases should be viewed with recognition that these phases, by the nature of the investigation, were not "steady states."

Temperature response (Figure 1). The temperature response showed rather wide individual variation in regard to time of onset, rate of ascent, peak level, duration of peak level, and rate of descent. All patients developed temperature elevation of some degree. The mean peak temperature achieved during the flush phase was 1.5° C (2.7° F) above base line.

[1] Kindly supplied as Pyrexal by the Wander Company, Chicago, Ill.

TABLE I

*Hemodynamic changes during pyrogen reaction**

	Study period				
	1	2	3	4	5
C.O.	6.49 (0.65)	6.74 (0.78)	7.13 (0.88)	8.26 (0.61)†	6.67 (0.36)
BAm	90.5 (4.1)	94.2 (3.8)	94.9 (5.0)	79.1 (4.5)	85.4 (4.2)
PAm	16.1 (1.2)	16.0 (0.9)	17.3 (2.2)	19.3 (1.6)‡	19.0 (1.3)‡
TSR	1,115.0 (117	1,118.0 (134)	1,065.0 (146)	766.0 (67)†	1,024.0 (82)
TPR	198.0 (33)	190.0 (29)	194.0 (23)	187.0 (20)	228.0 (16)
H.R.	77.0 (3)	77.0 (3)	92.0 (6)‡	98.0 (4)†	93.0 (4)†

* C.O. = cardiac output (1 per minute); BAm = mean brachial arterial pressure (mm Hg); PAm = mean pulmonary arterial pressure (mm Lg); TSR = total systemic resistance; TPR = total pulmonary resistance; H.R. = heart rate. Values given are group means with standard error of mean in parentheses.
† Differences significant at 0.01 level.
‡ Differences significant at 0.05 level.

Hemodynamic changes (Table I). Changes in cardiac output were variable during the prodrome, chill, and defervescent phases, but a significant elevation above control levels (average, + 27%) occurred during the flush.

Mean brachial arterial pressure did not change appreciably during the prodrome and chill phases, fell 14% below control levels during the flush phase, and rose toward base-line values with defervescence. Mean pulmonary arterial pressure showed no significant changes during the prodrome and chill phases. In contrast to the systemic pressure, however, pulmonary arterial pressure rose significantly above control values during flush and defervescence (Figure 2). This disparity in systemic and pulmonary pressure alterations was reflected in the respective resistance calculations. Total pulmonary vascular resistance remained essentially unchanged from control values during all phases, although a modest rise was noted during defervescence. Total systemic resistance fell significantly below control values during the flush (− 31%) and remained slightly depressed during defervescence.

The "wedge pressure" was measured in six patients during the control period, in two during the prodrome, in one during the chill phase, in six during the flush, and in seven during defervescence. All values were below 10 mm Hg. No increase greater than 2 mm Hg or decrease greater than 3 mm Hg from control values occurred in any patient.

TABLE II

*Changes in respiratory behavior during pyrogen reaction**

	Study period				
	1	2	3	4	5
$\dot{V}_{O_2}$	245.0 (27)	240.0 (10)	289.0 (22)†	311.0 (18)†	290.0 (15)†
$\dot{V}_E$	9,525.0 (665)	9,160.0 (650)	12,315.0 (1,395)‡	11,970.0 (800)†	11,885.0 (1,065)†
V_A	4,775.0 (420)	5,175.0 (440)	6,740.0 (940)‡	6,230.0 (520)†	6,070.0 (120)†
$\dot{V}_D$	4,740.0 (370)	4,425.0 (385)	5,485.0 (560)	5,745.0 (650)	5,685.0 (515)
R.R.	20.0 (1.4)	19.6 (1.5)	21.4 (1.6)	23.4 (1.2)†	23.5 (1.8)†
R.E.	39.0 (2)	38.0 (2)	43.0 (2)	39.0 (2)	41.0 (2)
T.V.	495.0 (37)	476.0 (29)	606.0 (83)‡	518.0 (50)	528.0 (50)
V_D/V_E	.50 (.02)	.48 (.03)	.47 (.03)	.47 (.02)	.49 (.03)
RQ	0.91 (.03)	0.89 (0.2)	0.95 (.01)	0.85 (.01)	0.88 (.04)

* V_{O_2} = oxygen uptake (cubic centimeters per minute, STPD); V_E = minute ventilation (cubic centimeters per minute, BTPS); V_A = alveolar ventilation (cubic centimeters per minute, BTPS); V_D = dead space ventilation (cubic centimeters per minute, BTPS); R.R. = respiratory rate; R.E. = respiratory equivalent (V_E/V_{O_2}); T.V. = tidal volume; V_D/V_E = dead space to minute ventilation ratio; and RQ = respiratory quotient. Values given are group means with standard error of mean in parentheses.
† Differences significant at 0.01 level.
‡ Differences significant at 0.05 level.

The heart rate paralleled the temperature response, being unchanged from control levels during the prodrome, increasing significantly during the chill (+ 19%), and remaining significantly elevated during the flush (+ 27%) and defervescent (+ 21%) phases. The calculated stroke volume did not deviate significantly from control levels during any study period.

Respiratory changes (Table II, Figure 3). The oxygen uptake was essentially unchanged during the prodrome, became significantly elevated above control levels during the chill phase, reached a peak level (+ 27%) during the flush, and remained significantly elevated during defervescence. Minute ventilation was unchanged during the prodrome, rose significantly above control levels during the chill phase (+ 29%) and remained significantly elevated during the flush (+ 26%) and defervescent (+ 25%) phases. Alveolar ventilation followed a sequence that was qualitatively identical to minute ventilation but quantitatively greater. Respiratory rate was unchanged during the prodrome, increased during the chill, and rose significantly above control levels during the flush and defervescent periods.

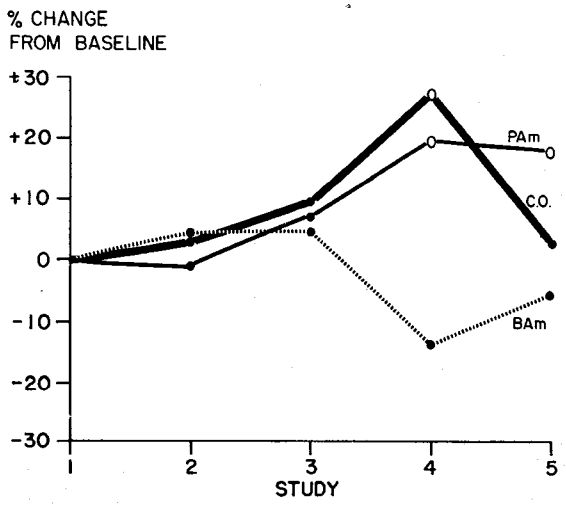

FIG. 2. CHANGES IN CARDIAC OUTPUT (C.O.), MEAN BRACHIAL ARTERIAL PRESSURE (BAM), AND MEAN PULMONARY ARTERIAL PRESSURE (PAM) DURING PYROGEN REACTION. Percentage of change, on ordinate; study period, on abscissa (1 = control; 2 = prodrome; 3 = chill; 4 = flush; 5 = defervescence). Plotted data represent group means. Open circles indicate changes which deviate significantly ($p = < 0.05$) from base-line values.

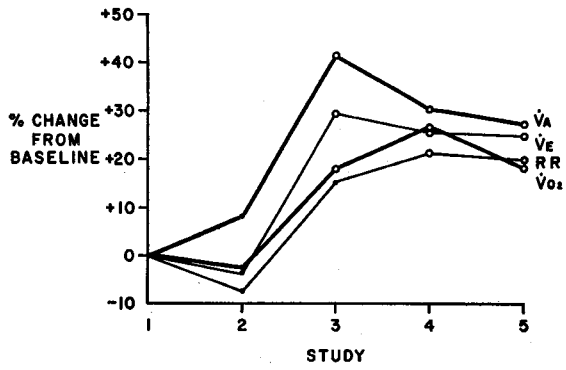

FIG. 3. CHANGES IN OXYGEN UPTAKE ($\dot{V}_{O_2}$), MINUTE VENTILATION ($\dot{V}_E$), ALVEOLAR VENTILATION ($\dot{V}_A$), AND RESPIRATORY RATE (RR). Same format as Figure 2.

The respiratory quotient, V_D/V_E ratio, and respiratory equivalent (minute ventilation/oxygen uptake) did not change significantly from control values during any study period. The tidal volume was significantly increased during the chill and remained elevated during flush and defervescence.

Arterial blood gas and pH changes (Table III). Neither the arterial oxygen saturation nor the carbon dioxide content deviated significantly from control levels during any postpyrogen study period. The calculated arterial carbon dioxide tension was unchanged during the prodrome, but fell significantly below control values during the chill, flush, and defervescent phases. The arterial pH rose minimally above control values during the chill, flush, and defervescent study periods.

The calculated alveolar oxygen tension and the arteriovenous oxygen difference were essentially unchanged during all study periods.

Chill versus no chill. With one exception, the data revealed that no statistically significant differences in hemodynamic, respiratory, or blood gas responses existed between the five patients who experienced frank chills and the five who did not. The exception was the significantly greater increase in alveolar ventilation during the chill phase in subjects with frank chills (see Figure 6). Other quantitative differences (not statistically significant) were noted. The group with frank chills demonstrated a greater rise in mean brachial and mean pulmonary arterial pressure, oxygen uptake, and minute and alveolar ventilation during the chill phase; a greater fall in mean brachial arterial pressure during the flush phase; and a greater

The period of temperature ascent (chill phase) was characterized by a rather wide scatter of individual hemodynamic responses. Altschule and associates (1, 2) mentioned alternate flushing and blanching of the capillary bed as a visible demonstration of the vasomotor instability characteristic of the chill phase. The unpredictable occurrence and severity of frank chills also contributes to such instability. The only consistent cardiac response during the chill phase was an increase in heart rate. Others have noted that a rather constant relationship exists between increase in cardiac rate and temperature elevation (11).

The erratic hemodynamic behavior during the chill phase contrasted with rather consistent respiratory changes. There was a significant increase in both minute and alveolar ventilation associated with a modest depression of arterial CO_2 tension. The hyperventilatory response during the chill phase appeared to be in excess of that needed to meet the increased metabolic demands imposed by the rising temperature. The fact that alveolar and minute ventilation both rose more sharply than oxygen consumption and that mild hypocapnia appeared both support this view. This hyperventilation may serve as a prompt means to achieve heat loss, as others have suggested (2, 5, 10). Previous workers have noted that alveolar hyperventilation and hypocapnia are more marked and prolonged than reported here when temperature elevation is achieved by methods which also block heat loss from the skin, i.e., in thermal chambers or in heated baths (5, 7, 26). That anxiety induced by discomfort may also contribute to hyperventilation cannot be discounted, however, since hyperventilation was more pronounced among those patients who experienced frank chills (Figure 6).

The flush phase was marked by consistent hemodynamic and respiratory alterations. An increase in cardiac output to 27% above the control level was accompanied by a drop in mean brachial arterial pressure but a rise in mean pulmonary arterial pressure. This disparate behavior of systemic and pulmonary arterial pressures suggests that the peripheral and pulmonary vascular beds do not participate equally in the vasodilation which characterizes the flush phase. Calculated total systemic resistance fell a significant 30% below control levels, while total pulmonary resistance was virtually unchanged. Since those wedge pressures obtained showed no change from base-line levels, it appears that the pulmonary arterioles, unlike those in the skin, the kidneys (4), and the splanchnic bed (22), do not dilate during the flush phase of the pyrogenic reaction. Although our data do not define the mechanism responsible for differences in systemic and pulmonary vascular behavior, the possible role of serotonin release during the pyrogen reaction merits consideration (11, 27). Our studies in man contrast with Kuida's demonstration of marked postcapillary pulmonary hypertension in animals (17). Aside from the possible effects of species variation and quite dissimilar experimental conditions, the differences may be attributed to the fact that the doses of pyrogen used by Kuida were massive when compared to those used in the present study.

The increase in cardiac output during the flush is accompanied by a parallel rise in cardiac rate. This tachycardia may have special clinical importance in terms of cardiac efficiency (28).

The increase in oxygen uptake reached its peak level during the flush phase, exceeding base-line values by almost one-third. However, minute ventilation and alveolar ventilation actually decline slightly from the values observed during the chill phase. This better parallelism between ventilation and metabolic demand may reflect the lessened demand for respiratory heat loss as the constricted, heat-retaining dermal vascular bed of the chill gives way to the dilated, heat-losing dermal bed of the flush phase. Thus, the alveolar hyperventilation of the chill phase moderates, and hypocapnia does not progress. Mean arterial oxygen saturation does not change significantly from base-line levels. Cullen, Weir, and Cook (6) had indicated that significant arterial desaturation accompanied temperature elevation. Our data agree with those of Gordon and associates (7, 26) and Altschule and co-workers (1, 2), who found no significant decrease in saturation.

During the phase of defervescence there was a gradual return toward base-line values. However, some burden upon the cardiopulmonary apparatus persisted. The heart rate remained significantly elevated, and the increase in pulmonary arterial pressure persisted. The oxygen uptake, minute ventilation, alveolar ventilation, and respiratory rate all remained significantly elevated, and mild hypocapnia continued.

Clinical implications of pyrogen reaction. The data presented clearly indicate that even the small doses of pyrogen used in this study impose an acute burden upon the cardiorespiratory apparatus. Despite the moderate degree of temperature elevation induced in these patients, they demonstrated increases in cardiac output, heart rate, oxygen uptake, and minute and alveolar ventilation in excess of 25% above base-line values. Furthermore, significant increases in the latter four appeared during the chill phase and persisted more than an hour after the temperature had begun to decline from its peak level. The clinical implications of these observations are clear. The acute demands imposed by a pyrogen reaction may be capable of provoking cardiac or respiratory failure in patients with diminished cardiac or pulmonary function.

The potential systemic hypotensive effect of pyrogens in normal subjects is also worthy of mention. Bradley, Chasis, Goldring, and Smith (4) have previously shown that this systemic hypotension can be quite marked and prolonged in hypertensive patients.

The extent of cardiopulmonary alterations elicited by these modest temperature increments confirms the experience of others that temperature elevation and pyrogen reaction are not equivalent terms (4, 11, 21). Although temperature changes, when present, can be used as a guide to the phases of the pyrogen reaction, the degree of temperature elevation is not a reliable guide to the degree of physiologic stress being imposed. Nor does the absence of significant fever in a patient exposed to some source of pyrogen assure that he will escape the cardiorespiratory alterations we have described. Furthermore, as Cranston (11) has stated, "it would appear unlikely that treatment with antipyretics should have much effect on cardiac failure induced by pyrogens." The current investigation indicates that this statement may be equally valid for patients with pyrogen-induced respiratory failure.

SUMMARY

1. Detailed cardiopulmonary studies were carried out in ten male subjects free of overt cardiopulmonary disease before and at four intervals after intravenous injection of a pyrogenic lipopolysaccharide extract of gram-negative bacilli.

2. Four phases of cardiopulmonary response could be identified following pyrogen injection corresponding to periods of stable temperature (prodrome), of rising temperature (chill), of peak temperature (flush), and of temperature return toward normal (defervescence).

3. No significant cardiopulmonary alterations occurred during the prodrome.

4. During the chill, flush, and defervescent phases, there was a significant elevation above control values in oxygen uptake, minute and alveolar ventilation, respiratory rate, and cardiac rate. A significant increase in cardiac output during the flush phase was associated with an increase in mean pulmonary arterial pressure but a decline in systemic pressure, indicating a difference in behavior of the pulmonary and systemic vascular beds.

5. The data indicate that the degree of temperature elevation cannot be used as a reliable guide to degree of cardiac or respiratory alteration induced by a pyrogen reaction.

6. It is concluded that the acute cardiopulmonary burdens imposed by a pyrogen reaction may be of sufficient magnitude to promote decompensation in patients with compromised cardiac or respiratory function.

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