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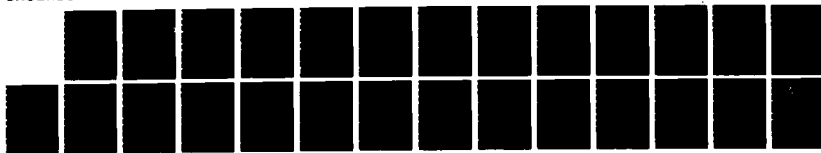
CUTANEOUS BLOOD FLOW AND LOCAL SWEATING AFTER SYSTEMIC
ATROPINE ADMINISTRATION(U) ARMY RESEARCH INST OF
ENVIRONMENTAL MEDICINE NATICK MA M A KOLKA ET AL
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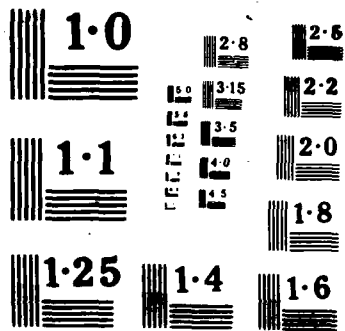
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19. Abstract (Cont'd)

the stimulation of increased cutaneous vasodilation is suggested to result by a combination of central and local responses which may be mediated through the release of vasoactive substances. *Abstract*

Localized cutaneous vasodilation (flush) is seen following systemic atropine administration. To verify calculated enhanced dry heat loss with actual changes in cutaneous blood flow, four men were studied in both control and atropine ($0.025 \text{ mg}\cdot\text{kg}^{-1}$; im) experiments ($T_a = 30^\circ\text{C}$, $T_{dp} = 7^\circ\text{C}$) during moderate exercise (55% $\dot{V}O_2$ peak). Esophageal temperature (T_{es}) and arm sweating (\dot{m}_s) by local dewpoint were measured continuously. Skin (forearm) blood flow (FBF) was measured twice each minute by venous occlusion plethysmography. Injection of atropine (2 mg) caused an increased sensitivity (+85%, $p < 0.01$) in FBF to T_{es} with no change in the vasodilator threshold. An elevated T_{es} onset (0.3°C , $p < 0.05$) for sweating occurred with no change in the sensitivity of \dot{m}_s to T_{es} (-27%, $p < 0.20$). No elevation in either forearm or \bar{T}_{sk} occurred before the onset of vasodilation, however, both mean skin (\bar{T}_{sk}) and local arm temperatures were higher in the atropine experiments after 15 minutes of exercise. Systemic atropine resulted in higher cutaneous vasodilation at the same core temperature with the local skin temperature following passively. The effect of systemic atropine in stimulation of increased cutaneous vasodilation is suggested to result by a combination of central and local responses which may be mediated through the release of vasoactive substances.

Key words: Anticholinergic drugs, evaporative heat loss, skin blood flow, thermoregulation

Neurogenic cutaneous vasodilation in humans has been suggested to be of cholinergic origin (Furchgott, 1984; Gaskell, 1956; Love et al., 1962; Rowell, 1983; Weiner et al., 1985). During passive heating of a cold subject, Roddie et al. (1957) observed an initial reduction in vasoconstrictor tone followed by active vasodilation as the core temperature increased above a threshold temperature. The first phase of this biphasic increase in forearm cutaneous blood flow did not respond to arterial atropine injection and appeared to be solely a release of adrenergic vasoconstrictor tone. The major part of forearm cutaneous vasodilation appears in the second phase, which can be blocked by local atropine administration, and is often associated with (or attributed to) active cholinergic vasodilation (Johnson et al., 1973; Roddie, 1983; Rowell, 1983).

During heat stress, systemic atropine administration has been suggested to dilate cutaneous vessels by a yet unknown mechanism. Several studies have reported a "flush" and/or increased skin conductance after atropine has inhibited sweating during exercise in the heat. This "flush" may be a compensatory vasodilator response to offset the rise in body temperature (Weiner et al., 1985); or may be unrelated to cholinergic blockade. In previous experiments from our laboratory, we have consistently demonstrated higher sensible heat loss (non-evaporative, R + C) after systemic atropine administration suggesting enhanced cutaneous vasodilation (Gonzalez et al., 1986; Kolka et al., 1984). Likewise, Davies et al. (1978) have reported similar findings.

In this paper, we report the effect(s) of systemic atropine treatment on the control of forearm cutaneous blood flow as measured by venous occlusion plethysmography during exercise in a moderate environment. We have simultaneously measured cutaneous blood flow with local sweating rate to investigate physiological mechanisms responsible for the atropine flush. The environment was chosen so that no significant resting vasodilation would occur (Rowell, 1983).

METHODS

Subjects Four males volunteered for the study following consent procedures passed by our local Human Use Committee. Their physical characteristics are given in Table 1.

Protocol Testing occurred in the late fall when subjects were not heat acclimated. All subjects were familiarized with all testing and measurement procedures before data collection began. Subjects were tested on 2 occasions in an ambient temperature (T_a) of 30°C with an ambient water vapor pressure (P_w) equal to 1.0 kPa; once after the intramuscular injection of atropine sulfate (0.025 mg·kg⁻¹; Elkin-Sinn, Cherry Hill, NJ) and once after the injection of an equal volume of sterile saline. Test days were separated by a minimum of 48 h, order of drug presentation was counterbalanced. Experiments were conducted between 0700 and 1000h, with any one subject tested at the same hour each day to control for circadian variation in heat loss responses (Stephenson et al., 1984). Subjects had not eaten the previous 12h before testing, and were not aware of the specific drug being injected.

Physiological Variables The subjects exercised at 55% of a previously determined $\dot{V}O_2$ peak while seated behind a cycle ergometer. Total exposure time was 65 minutes, which included: a five minute baseline period before injection after thermal equilibrium (constant \bar{T}_{sk} and T_{es}) had been accomplished, the injection of the appropriate drug, an additional 30 minutes of rest, and 30 minutes of submaximal exercise. The subject entered the chamber, was weighed and then rested in the chair of the modified ergometer. He placed a catheter containing a thermocouple in his esophagus at the level of the heart

for the measurement of core (esophageal) temperature (T_{es}) and was required to drink 200 ml of water at this time. Thermocouples were placed on the skin at eight sites to estimate \bar{T}_{sk} (Nishi, et al., 1970); one site being the forearm ($T_{s,a}$) where blood flow and sweating were measured. An automatic dew point sensor enclosed in a ventilated capsule was attached to the volar surface of the forearm which was used to determine local sweating rate (\dot{m}_s) (Graichen et al., 1982). A mercury-in-silastic strain gauge was placed on the forearm for the measurement of forearm blood flow (FBF) by venous occlusion plethysmography (Hokanson et al., 1975; Whitney, 1953). Temperature and sweating were continuously recorded and FBF was measured twice each minute. Heart rate (HR) and blood pressure on the contralateral arm were measured each 2.5 minutes by an automatic auscultatory method (Accu-Torr) and metabolic heat production (M) was estimated at 20 minutes of rest (15 min post injection) and at both 10 and 25 minutes of exercise. The T_{es} thresholds for cutaneous vasodilation and sweating were calculated for each experiment by analyzing the exercise transient phase of the FBF to T_{es} and \dot{m}_s to T_{es} relationships. The exercise transient phase is defined as the time of exercise during which a rapid inflection in T_{es} , sweating rate, and FBF was observed. A regression equation was calculated for each subject during the exercise transient for both FBF to T_{es} and \dot{m}_s to T_{es} . Oftentimes FBF decreased as T_{es} rose; in these cases such data, as well as the data collected after T_{es} reached a steady level, were not included in the linear regression equation. The T_{es} threshold for the initiation of sweating was calculated from the regression equation at a threshold of $\dot{m}_s = 0.06 \text{ mg} \cdot \text{cm}^{-2} \cdot \text{min}^{-1}$ (Buettner, 1959). The T_{es} threshold for the initiation of cutaneous vasodilation was calculated from the regression equation at the average resting FBF for each subject.

Statistical Analysis

All data were analyzed by a two-way ANOVA with repeated measures. Post-hoc tests (Tukeys) were performed whenever a significant F ratio appeared ($p < 0.05$). All differences reported in the RESULTS are significant at $p < 0.05$.

RESULTS

Mean thermoregulatory data for both rest and exercise are presented in Table 2. There were no differences in any resting variables between the saline and atropine experiments. However, after 25 minutes of exercise, T_{es} , \bar{T}_{sk} , HR and FBF were all higher in atropine experiments, with forearm sweating being reduced. The increase in T_{es} ($^{\circ}\text{C}\cdot\text{min}^{-1}$ during transient) averaged 0.08 (± 0.02) in saline experiments and 0.07 (± 0.01) in the atropine experiments. Heat storage was not more rapid after atropine treatment than control experiments. However, the rate of heat loss was not proportional to heat production, and consequently a thermal steady-state was not reached. Esophageal temperature averaged 37.4 (± 0.1) $^{\circ}\text{C}$ in control experiments and 37.8 (± 0.2) $^{\circ}\text{C}$ in atropine experiments by 25 minutes of exercise (Table 2).

The relationship for FBF and esophageal temperature during the exercise transient is shown for a single subject in Figure 1. Table 3 presents the calculated slopes (sensitivity) and vasodilatory thresholds for all subjects. There was no change in the vasodilator threshold, however, there was an average 85% (range 34-275%) elevation in the slope of FBF to T_{es} during the atropine experiments. This vasodilation in atropine treated subjects occurred before any measurable changes in \bar{T}_{sk} or $T_{s,a}$ which were then observed to follow passively. Figures 2A and 2B show the time course of forearm blood flow and forearm temperature during the saline and atropine experiments for the same subject. It should be noted that Figures 2A and 2B employ different Y-axis calibration.

The calculated slopes and T_{es} thresholds for initiation of active sweating (\dot{m}_s) are given in Table 4. There was no significant reduction in the slope (-27%, $p = 0.20$) as a consequence of the systemic atropine administration. We expected significance as atropine acts peripherally (binding at the cholinergic receptors on the sweat gland) and the thermoregulatory axiom of peripheral action generally is associated with a suppression in the slope of sweating to elevation in T_{es} . However, the T_{es} threshold for \dot{m}_s was shifted by an average of 0.3°C higher. The times (min) to onset for both vasodilation and sweating after the start of exercise are given in Table 5. In all four subjects, the sweating onset preceded vasodilation in the control but not the atropine experiments. FBF vasodilation occurred almost 4 minutes earlier during experiments after atropine injection compared to control, whereas the onset time of sweating was delayed by 6 minutes. The average exercise cutaneous blood flow for all subjects after the initial transient period was $10.4 (\pm 2.0)$ and $17.5 (\pm 6.0) \text{ ml} \cdot 100\text{ml}^{-1} \cdot \text{min}^{-1}$ for the control and atropine experiments, respectively.

DISCUSSION

Atropine exhibited two responses in the present study: 1) sweat secretion was blocked; and 2) vasodilation was potentiated. The mechanism by which atropine blocks sweat secretion has been known for many years, owing to its competitive inhibition of acetylcholine (ACh), a neurotransmitter of the muscarinic post-ganglionic cholinergic neuron (Weiner *et al.*, 1985). In our study, the systemic dose of atropine was sufficient to block cholinergic sweat gland activity and as would be expected, a higher onset temperature for regulatory sweating was apparent in conjunction with a delay in the time of sweating onset after the start of exercise.

There have been many reports of enhanced cutaneous vasodilation, either measured directly or calculated from heat balance data, following atropine treatment. These reports include: a "mantle flush" (Weiner et al., 1985), acetylcholine independent vasodilation in response to body heating (Roddie et al., 1957) after intraarterial atropine injection, and enhanced dry heat loss in the more recent experiments of Davies et al. (1978) and Kolka et al. (1984) during exercise with systemic administration. The mechanism(s) by which atropine increased cutaneous vasodilation is not presently known. These may involve (1) a direct local action at the blood vessel, (2) a central release of vasoconstriction or facilitation of heat loss, (3) the presence of vasodilatory substance(s) associated with the sweat gland, or any combination of these effects.

Local Action of Atropine

The mechanism responsible for the increased cutaneous radiative and convective heat loss (R+C) after atropine treatment is not wholly apparent. Roddie et al. (1957) presented evidence that atropine infused intraarterially (0.3mg) resulted in a delayed onset of forearm vasodilation in response to body heating. This response was interpreted as putative evidence that vasodilatory fibers were cholinergic. However, in the same report, intraarterial atropine had no effect on forearm blood flow when atropine was given following the vasodilation in response to body heating. Yet, the atropine was effective in blocking the vasodilatory response induced by acetylcholine given subsequently. These findings were interpreted as indicating that the vasodilation had been mediated through noncholinergic fibers; alternatively, Roddie suggested that such vasodilation owed its effect to the release of a vasodilatory substance. Since vasodilation occurred during atropinization with no response to added acetylcholine, one possible explanation could be that the vasodilation occurred at

level distinct from the endothelium as recent in vitro studies of mammalian arteries clearly indicate that acetylcholine activates a muscarinic receptor on the endothelial cells to initiate relaxation of arterial smooth muscle (Furchgott, 1984). It has also become clear that other vasoactive substances which act in a similar manner as acetylcholine are dependent on an intact endothelium (Furchgott, 1984). Furthermore, there is some, albeit limited, evidence that arterioles respond to acetylcholine by a similar mechanism which is independent of prostaglandins (Moncada et al., 1985). These findings together with the observation (s) of Roddie et al. (1957) point to other mechanisms for vasodilation which may be independent of cholinergic blockade.

Release of Vasoconstrictor Activity

The increase in FBF shown in our subjects may be attributed to an effect of atropine at the level of the spinal ganglia (nicotinic) or higher level CNS, simply inhibiting vasoconstrictor tone (Weiner et al., 1985). However, the marked (85% average) increase in the sensitivity of FBF to T_{es} appears to be greater than can be accounted for than by a release of adrenergic vasoconstriction, as Wenger et al. (1986) have recently shown during brachial nerve block. In their studies, forearm blood flow was measured after sympathetic nerve block at rest as the skin temperature was manipulated. Forearm cutaneous blood flow was measured at skin temperatures similar to the present study (32.5 or 35°C); and after the release of vasoconstrictor activity, cutaneous blood flow was elevated only 2 ml·100 ml⁻¹·min⁻¹ at a constant core temperature. In our study, the increase in forearm cutaneous blood flow was much greater than 2 ml·100 ml⁻¹·min⁻¹ (Fig. 1) at a constant core temperature.

A central thermal action of atropine, possibly facilitating dopaminergic pathways, for heat dissipation needs also to be evaluated (Boulant, 1980), perhaps in conjunction with a central release of vasoconstriction, as we found a shorter

delay in onset time for cutaneous vasodilation to enable dry heat loss. Also evident from our data was the finding (Table 5), that sweating onset time was later in the atropine experiments.

Vasoactive Intestinal Polypeptide

The innervation of the eccrine sweat gland (Heinz-Erian et al., 1980; Vaalasti et al., 1985) is similar to the salivary gland, which has been studied extensively (Burnstock, 1985; Hokfelt et al., 1980; Lundberg et al., 1980; Uddman et al., 1980; Wharton et al., 1980). Both exocrine glands are innervated by postganglionic cholinergic neurons, with the difference between the two being the type of innervation. The eccrine sweat glands are innervated by the sympathetic nervous system, while the salivary glands are innervated by the parasympathetic nervous system. The cholinergic neurons of both glands contain two neurotransmitters, Ach and vasoactive intestinal peptide (VIP) (Burnstock, et al., 1985; Hokfelt et al., 1980; Lundberg et al., 1982; Vaalasti et al., 1985; Wharton et al., 1980).

Lundberg et al. (1980) have presented an hypothesis for regulation of vasodilation and secretion in exocrine glands, using the cat submandibular salivary gland as a functional model. They have proposed that postganglionic neurons release Ach and VIP concomitantly, with Ach activating the gland via muscarinic receptors to secrete saliva and VIP clearly stimulating atropine-resistant vasodilation. The mechanism for secretion from the eccrine sweat gland and vasodilation around the gland may be similar to the salivary gland. For example, sweat glands are located in the subdermal connective tissue with the body of the gland being approximately 2 to 5 mm beneath the epidermis (Quinton, 1983), but the reabsorptive duct penetrates the epidermis to open on the skin surface. VIP-like immunoreactive and acetylcholinesterase-positive

neurons follow and touch blood vessels surrounding the eccrine sweat glands with VIP-like neurons supplying both the secretory acini and the reabsorptive ducts (Heinz-Erian *et al.*, 1985; Vaalasti *et al.*, 1985). VIP may be responsible for the faster onset time and greater sensitivity of cutaneous vasodilation that we observed with atropine treatment in the present study. A greater amount of VIP available for diffusion to the blood vessels has been found surrounding the salivary gland (Lundberg *et al.*, 1982; Wharton *et al.*, 1980) and quite possibly both Ach and VIP release would occur at the sweat gland in response to elevated core and surface temperatures. The close relationship between the onset of cutaneous vasodilation and sweating observed previously (Love *et al.*, 1962) may be explained by the coexistence of VIP and Ach in the neurons supplying eccrine sweat glands. However, VIP alone may not adequately explain the potentiated vasodilation observed with atropine treatment and further experimentation addressing this hypothesis is warranted.

The present study, together with the evidence that vasodilation can occur via prostaglandin-mediated mechanisms (Moncada *et al.*, 1985) suggests that the vasodilation observed during exercise after atropine treatment may be distinct from the acetylcholine and acetylcholine-like mediated vasodilation which requires an endothelium derived relaxing factor. Furthermore, it is possible that the vasodilation which occurs (in spite of the anticholinergic effect of atropine on sweat glands) may be mediated by the release of a vasoactive substance (perhaps VIP), which is independent of an endothelially derived relaxing factor.

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The views, opinions and/or findings contained in this report are those of the authors and should not be construed as official Department of the Army position, policy, or decision, unless so designated by other official documentation.

Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on the Use of Volunteers in Research.

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Figure Legends

Figure 1. Forearm blood flow as a function of esophageal temperature during the exercise transient in one individual during saline (●) and atropine (○) experiments. Local skin temperature of the forearm was 33.2°C in the saline experiments and 33.9°C in the atropine experiments at the initiation of vasodilation in this subject. Mean skin temperature was 34.0 °C and 34.1°C, respectively.

Figure 2A and 2B. Forearm blood flow and forearm skin temperature as a function of time during exercise (55% $\dot{V}O_2$ peak) for saline (top panel) and atropine (lower panel) experiments. Drug injection occurred at 5 minutes, exercise was initiated at 35 minutes and was ended at 65 minutes.

Table 1. Individual characteristics of the subjects.

	Age	Ht	Wt	$\dot{V}O_2$ peak	A_D^\dagger
	(yr)	(cm)	(kg)	(l·min ⁻¹)	(m ²)
1	22	185.4	88.3	4.11	2.12
2	20	170.2	67.0	3.47	1.78
3	19	181.0	87.0	3.97	2.08
4	24	191.8	82.8	3.28	2.12
	21.3(2.2)	182.1(9.1)	81.3(9.8)	3.71(0.40)	2.03(0.16)

† DuBois surface area

Table 2. Resting and 25th minute exercise temperature data for control experiments and following atropine administration.

	<u>Rest</u>		<u>Exercise</u>	
	Control	Atropine	Control	Atropine
Esophageal temperature (°C)	36.7(0.2)	36.6(0.2)	37.4(0.2)	37.8(0.2)*
Mean weighted skin temperature (°C)	34.0(0.3)	34.1(0.3)	33.6(0.5)	35.7(0.5)*
Arm sweating rate (mg·cm ⁻² ·min ⁻¹)	0.16(0.06)	0.16(0.04)	1.08(0.3)	0.43(0.14)*
Forearm blood flow (ml·100ml ⁻¹ ·min ⁻¹)	1.8(0.8)	1.8(0.5)	9.2(0.4)	17.1(5.7)*
Metabolic rate (W·m ⁻²)	48.3(1.7)	38.3(1.8)	368.4(38.3)	341.8(48.3)
Heart rate (b·min ⁻¹)	67(8)	59(13)	130(5)	158(4)*
Mean arterial pressure (kPa)	12.3(1.3)	11.1(0.7)	13.7(0.4)	13.6(2.0)

Values are Mean ± SD.

*Different from control (p < 0.05)

Table 3. T_{es} threshold for initiation of cutaneous vasodilation and slope of linear regression equation generated from the transient response to exercise.

<u>Subject</u>	<u>T_{es} threshold ($^{\circ}C$)</u>		<u>Slope</u>	
	<u>Saline</u>	<u>Atropine</u>	<u>Saline</u>	<u>Atropine</u>
1	36.92	36.67	18.90	25.39
2	36.14	36.54	7.17	26.50
3	36.86	36.80	13.00	26.90
4	37.09	36.90	21.00	32.10
\bar{X} (SD)	36.75(0.42)	36.73(0.16)	15.02(6.23)	27.72(2.99)*

T_{es} , esophageal temperature

* Significantly different from saline, ($p < 0.05$)

Table 4. T_{es} threshold ($^{\circ}C$) for sweating and slopes of linear regression equation generated from the transient response to exercise.

<u>Subject</u>	<u>T_{es} threshold</u>		<u>Slope</u>	
	<u>Saline</u>	<u>Atropine</u>	<u>Saline</u>	<u>Atropine</u>
1	36.78	36.81	1.31	1.18
2	36.37	36.51	0.82	0.82
3	36.26	36.85	0.84	0.75
4	36.54	37.06	1.38	0.45
\bar{X} (SD)	36.49(.23)	36.81(.23)*	1.09(.30)	.80(.30)

T_{es} , esophageal temperature

*Significantly different from saline, $p < 0.05$.

Table 5. Time (minutes) of effector onset after initiation of exercise.

<u>Subject</u>	<u>Vasodilation onset</u>		<u>Sweating onset</u>	
	<u>Saline</u>	<u>Atropine</u>	<u>Saline</u>	<u>Atropine</u>
1	7.5	3.5	5.0	6.0
2	6.0	2.5	0.5	4.0
3	5.5	2.0	1.5	9.0
4	5.5	1.5	1.5	15.0
\bar{X} (SD)	6.1(0.9)	2.4(0.9)*	2.1(1.9)	8.5(5.8)*

*Different from saline, ($p < 0.05$).

Figure 1.

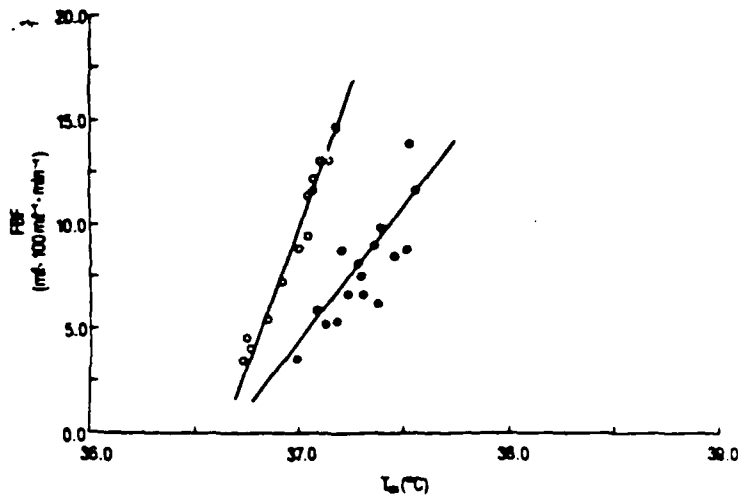


Figure 2a.

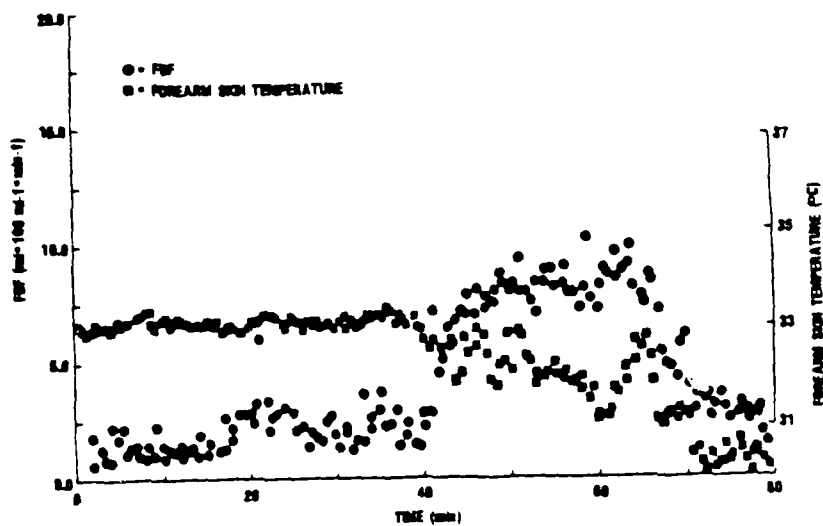
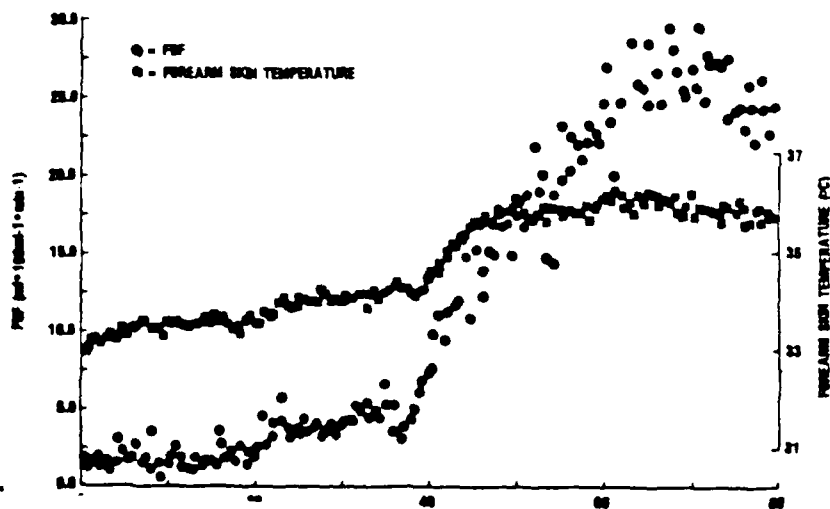


Figure 2b.



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