Heparin, free fatty acids and an increased metabolic demand for oxygen

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Summary

Obese and lean subjects were given heparin with or without Intralipid in order to assess the effect of heparin on plasma concentration of free fatty acids (FFA) and oxidative metabolism. The FFA response depended on the triglyceride concentration and was associated with a prompt rise in oxygen consumption. Plasma catecholamines did not alter after heparin and the increase in oxygen uptake was proportional to the rise in FFA. The use of heparin, therefore, has metabolic disadvantages which may outweigh the potential benefits, for example in the management of myocardial infarction where heparin may increase the metabolic demand on the heart by increasing FFA levels.

Introduction

Heparin is used not only for the treatment of pulmonary emboli but often as an adjunct to the management of myocardial infarction. However, heparin has a potent metabolic effect in addition to its antithrombotic action: it is known to activate lipoprotein lipase (Connor and Armstrong, 1961) which will release free fatty acids (FFA) from both stored and circulating triglyceride (TG). The heparin-induced rise in plasma FFA may increase the metabolic rate and this in turn may increase the demand for oxygen by the body's tissues. This could be detrimental in conditions such as myocardial infarction where a reduction in tissue oxygen demand is a major clinical objective.

The authors investigated the metabolic responsiveness of obese and lean subjects to changes in FFA induced by the injection or infusion of heparin in doses similar to those used clinically. The results show an appreciable increase in the body's demand for oxygen after heparin and these observations may, therefore, have clinical relevance.

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Patients and methods

Eight obese and 6 lean subjects were investigated on an out-patient basis. All were normotensive and euthyroid women. These obese women were aged 43.6 ± 5.0 years (mean $\pm$ s.e. mean) and weighed 100.5 ± 5.4 kg, i.e. on average 80% above the ideal body weight (IBW). The lean women were of similar age (46.3 ± 6.4 years) and weighed 49.2 ± 1.5 kg, i.e. 11% below IBW. IBW was defined as that corresponding to the midpoint of the weight range for medium frame size as listed in the weight for height tables of the Metropolitan Insurance Company (1968).

The resting oxygen consumption (RO_2) and CO_2 output were monitored at one-min intervals by the ventilated hood technique, after the subjects had fasted for 12 hr and rested supine for 30 min. The oxygen consumption per min was expressed in equivalent units of heat production, i.e. in kJ/min.

After a preliminary measurement of RO_2 for 30 min, 6 of the subjects, 3 normal weight and 3 obese, were given a bolus of 5000 i.u. heparin i.v. and the change in oxygen consumption monitored at one-min intervals for a further 2 hr. To induce greater rises in plasma FFA concentrations, the remaining subjects were infused i.v. with variable amounts (50 to 300 ml) of Intralipid 10% (Vitrum®), and were given an i.v. bolus of 5000 i.u. heparin. To measure the effect of triglyceride infusion alone on oxygen consumption, 3 subjects were also infused with 10% Intralipid at 2.5 ml/min for one hr.

Venous blood was taken from the other brachial vein with an Abbott 19 g Butterfly cannula, a few ml of sodium citrate BPC being used to keep the cannula patent. Blood for the estimation of plasma FFA was transferred to ice-cold tubes containing Na EDTA, the plasma FFA being measured by titration (Trout, Estes and Friedberg, 1960). Triglyceride was measured with a Boehringer-Mannheim enzymatic system (No. 125032). Blood for catecholamines was also obtained from 5 lean and 5 obese

FIG. 1. The relationship between the maximum rise in oxygen consumption expressed in kJ/min and the absolute increase in plasma free fatty acids ($\mu\text{mol/l}$) 30 min after heparin injection ($r=0.84$). The geometric regression line for both the obese and lean subjects is shown ($y=0.0047 x^{0.58}$). ●=obese subjects; ○=lean subjects.

subjects before and 30 min after the heparin injection. The plasma catecholamines were measured by a radioenzymatic technique (Callingham and Barrand, 1979). Ethical approval and fully informed consent was obtained.

Results

The infusion of Intralipid alone raised the plasma triglyceride concentration from 0.80 ± 0.37 to 2.12 ± 0.99 mmol/l. Oxygen consumption showed no significant change (4.65 ± 0.33 kJ/min before and 4.73 ± 0.46 kJ/min after one hr of Intralipid infusion).

On injecting heparin, however, the resting oxygen consumption increased promptly to reach a plateau at 30 min. The peak rise in oxygen consumption was correlated with the increase in plasma FFA at 30 min, i.e. when there was a plateau in oxygen consumption. For the 14 subjects, this relationship (Fig. 1) was curvilinear ($r=0.84$; $P<0.001$) and the equation which best fitted was as follows: $y=0.0047 \times x^{0.58}$ where y = rise in oxygen consumption in kJ/min and x = rise in plasma FFA in mmol/l. Both lean and obese groups separately showed a significant relationship ($r=0.89$, $P<0.02$; $r=0.84$, $P<0.01$ respectively) but there was no significant difference in their responses. In those given heparin alone after a 12-hr fast the FFA response related to the initial triglyceride level ($r=0.85$, $P<0.05$) and resulted in a rise in oxygen consumption by as much as 0.34 kJ/min. In both the lean and obese groups,

heparin did not alter either plasma noradrenaline (Table 1) or adrenaline.

TABLE 1. The plasma catecholamine concentrations before and after heparin

	Lean (5)		Obese (5)	
	Before	After	Before	After
Plasma noradrenaline (nmol/l)	2.50 $\pm$ 0.47	2.18 $\pm$ 0.54	2.04 $\pm$ 0.32	1.71 $\pm$ 0.49
Plasma adrenaline (nmol/l)	0.13 $\pm$ 0.03	0.13 $\pm$ 0.04	0.05 $\pm$ 0.02	0.04 $\pm$ 0.01

Subject numbers in parentheses (mean $\pm$ s.e. mean).

Conversion: SI to traditional units—plasma noradrenaline 1 nmol/l $\equiv$ 0.17 ng/ml; plasma adrenaline 1 nmol/l $\equiv$ 0.73 ng/ml.

Discussion

The suggestion that heparin induces an increase in metabolic rate by increasing circulating FFAs is consistent with the recognition that FFAs stimulate the metabolism of *in vitro* preparations of both liver (Krebs, 1972) and renal cortex (Lee, Vance and Cahill, 1962). Although other mechanisms relating to catecholamine release could have been responsible for the metabolic response in the present subjects, no appreciable change in either hormone was found

after i.v. heparin, so a direct thermogenic stimulus to metabolism by these hormones is unlikely. The increase in oxygen consumption after heparin was related to the rise in FFA in curvilinear fashion, this relationship becoming more linear when the rise in plasma FFA was more than 1000 $\mu\text{mol/l}$. Previous isotopic work had demonstrated a linear relationship between the rate of FFA oxidation and the actual plasma FFA concentration but this was only shown over a 1000 $\mu\text{mol/l}$ rise in FFA (Issekutz *et al.*, 1968). A similar response in oxygen uptake to a rise in FFA was found in both lean and obese subjects (Issekutz *et al.*, 1968), as confirmed by the present work. However, the obese may be expected to have a greater metabolic response to heparin because of the greater availability of circulating triglycerides.

The increase in plasma FFA seems to depend not only on the concentration of plasma triglyceride but also on the dose of heparin used and its route of administration. Heparin given subcutaneously at a dose of 5000 i.u. after a fatty meal will raise the plasma FFA up to 2000 $\mu\text{mol/l}$ while 15 000 i.u. given i.v. can produce an increase in plasma FFA to over 5000 $\mu\text{mol/l}$ (Nordoy *et al.*, 1977). Such an increase can be expected to increase the metabolic rate by 0.7 kJ/min or 25%. Although Connor and Armstrong (1961) showed that heparin (5000 i.u.) given as an i.v. bolus rather than as a subcutaneous dose, results in a greater initial rise of both plasma lipoprotein lipase and glycerol, the effects of the i.v. heparin lasted only 6 hr. In contrast, heparin given subcutaneously produced a persistent increase in the plasma lipoprotein lipase and glycerol for 24 hr.

These metabolic effects of heparin on plasma FFA concentrations and oxygen uptake may prove disadvantageous in several clinical conditions. In myocardial ischaemia, the development of infarction is a progressive process which can be modified by reducing myocardial oxygen requirements. Recently it has been shown that the oxygen consumption of the myocardium is increased by elevated FFA without an improvement in its mechanical function (Simonsen and Kjekshus, 1978). The present data suggest that the use of i.v. heparin not only increases the peripheral oxygen requirements in the fasted state but more so in the fed state: this would therefore lead to a demand for an increased cardiac output (Bevegård and Shepherd, 1967). If cardiac arrhythmias are induced by a high plasma FFA (Kurien and Oliver, 1970) then heparin may also complicate the management of patients with a myocardial infarct (Opie, Tansey and Kennelly, 1977). The FFA response to elevated plasma concentrations of adrenaline in patients with a myocardial infarct (Siggers, Salter and Fluck, 1971) can be blocked with a β -adrenergic blocking drug but this blockade would not limit the FFA response to heparin. Thus

there is a need to balance the potential benefits accruing from diminished thrombotic function with the metabolic disadvantages of heparin and it would certainly seem wise to limit the use of heparin in obese patients known to have hypertriglyceridaemia.

A further use for heparin is in association with the parenteral feeding of lipid preparations. The authors' observations show no effect of triglyceride infusion on the metabolic rate but the combination of both Intralipid and heparin may be expected to produce a very large increase in plasma FFA. This could be detrimental as suggested by the recent report of 20 deaths from myocardial infarction in heparinized subjects receiving Intralipid during haemodialysis (Bergrem and Lievestad, 1978).

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