

Effect of Prolonged Starvation on the Functional Status of the Isolated Rat Atria¹ (36765)

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We have previously demonstrated that isolated atria from 24 hr starved rats show a smaller rate of decline of the force of contraction with time, when incubated in the absence of exogenous substrate than atria from fed rats (1). This was interpreted as indicating that starvation for 24 hr results in the accumulation of endogenous substrates by the atria useful for the contractile process when placed in a substrate-free environment. Such an interpretation is consistent with biochemical data indicating that during starvation the heart accumulates lipid which apparently is used to support various energy requiring processes *in vitro* (2).

The present report is a continuation of studies dealing with the effect of starvation on cardiac function. In particular, atrial function was assessed after starvation periods of 1 to 6 days. Only 5 of 20 rats survived 6 days of starvation so this represents a very critical situation comparable to months of starvation for the human (3).

The functional status of atria from starved rats was assessed in two ways (a) the absolute developed tension was determined after a 1 hr period in Krebs-Henseleit medium containing glucose and compared to the tension developed by atria from fed rats, and (b) the rate of decline of developed tension when placed in the above medium but in the absence of glucose or any other energy-yielding substrate was determined for atria from fed and starved rats. The former way evaluates

the effects of starvation on the contractile machinery of the atria while the latter method assesses the effect of starvation on the availability of endogenous substrates to support the developed tension.

Methods. Male, Sprague-Dawley rats, weighing 180–200 g, which either had *ad libitum* access to food and water (fed) or were without food for 1 to 6 days (starved) were employed. Atria were removed from decapitated rats and suspended in 50 ml of modified Krebs-Ringer bicarbonate glucose medium (4) of the following composition (mM): NaCl, 120; KCl, 4.8; CaCl₂, 1.22; MgSO₄·7H₂O, 1.33; KH₂PO₄, 1.2; NaHCO₃, 25.3; glucose, 5.55. The atria were electrically stimulated at 200/min in this medium and aerated with 95% O₂ and 5% CO₂ to maintain a pH of 7.4 at 30°. The developed tension of atria was determined as previously described by Ko and Paradise (5).

An equilibration period of 1 hr was allowed in the above medium before readings were taken. The experimental values of contractility (peak tension) were compared with those of control records obtained at zero time (following equilibration) and expressed as percentage change in developed tension.

In the experiments with substrate-free medium, the normal medium was changed to substrate-free medium (*i.e.*, free of glucose) following the 1 hr equilibration period.

Results. Effect of starvation on body weight of rats. Figure 1 shows that the body weight of starved rats decreased markedly with time. Some rats began to die after 4 days starvation. In contrast, the body weight of fed rats increased with time.

Effect of starvation on developed tension of

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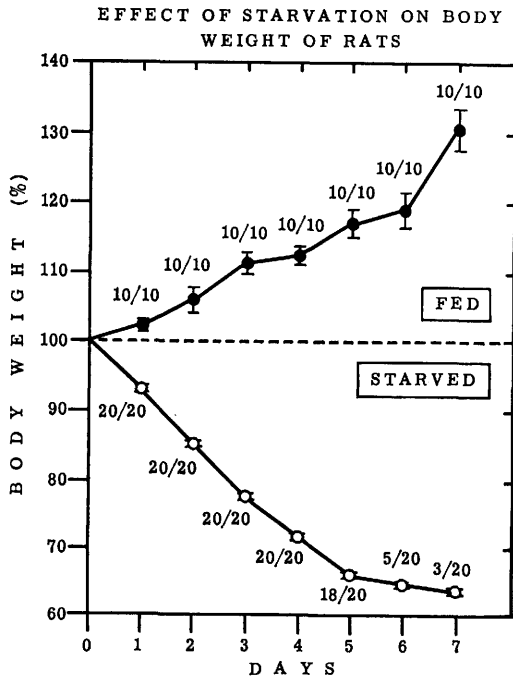


FIG. 1. Effect of starvation on percentage change in body weight of rats. Vertical bars represent ± 1 SE. Numbers next to each point on the graph indicate the number of rats that survived relative to the total number studied, e.g., after 6 days of starvation only 5 to 20 rats survived.

atria. The developed tension of atria incubated for 1 hr in normal glucose-containing medium is shown in Table I. In every case atria from starved animals developed tensions as great or greater than atria from fed animals.

Effect of starvation on rate of decline of developed tension of atria in substrate-free medium. Figure 2 shows the effects of omission of exogenous substrate from the medium on the tension developed by atria from starved and fed rats, following a 1 hr equilibration period in the normal Krebs-Ringer

bicarbonate glucose medium. It is evident from Fig. 2 that when the atria from starved rats are suspended in substrate-free medium, the atria from rats starved for 2 days have a significantly smaller reduction in contractility than do those from shorter (1 day) or longer (3 to 6 days) periods of starvation. It is also evident from the figure that all groups of atria from starved rats show less depression of the force of contraction in substrate-free

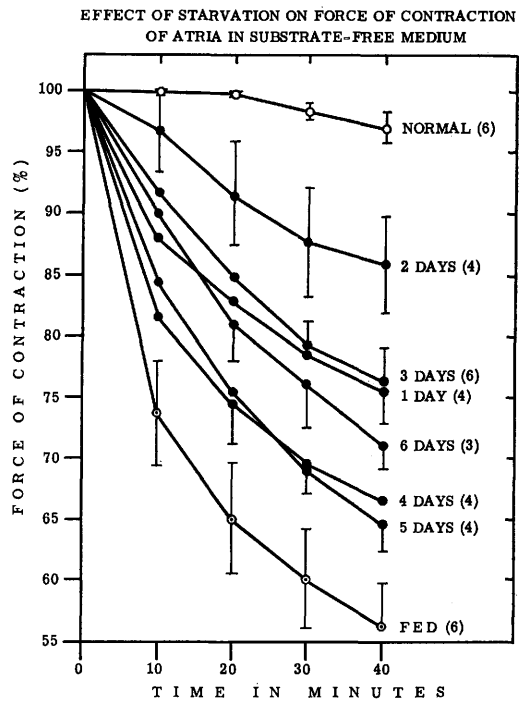


FIG. 2. Effect of starvation on force of contraction of atria in substrate-free medium. Normal represents force of atria from fed rats in the normal glucose-containing medium. All other curves represent forces of atria from fed or starved (1 to 6 days) rats incubated in normal medium for 1 hr then exposed to glucose-free medium for an additional 40 min. Values in parentheses represent number of experiments.

TABLE I. Developed Tension Magnitude (mg) of Atria from Starved and Fed Rats.

Fed	Starvation (days)					
	1	2	3	4	5	6
412 \pm 21 ^a (13) ^b	493 \pm 29 (10)	497 \pm 19 (8)	619 \pm 50 (4)	511 \pm 55 (4)	619 \pm 62 (4)	513 \pm 80 (4)

^a Mean \pm SE.

^b Values in parentheses represent number of experiments.

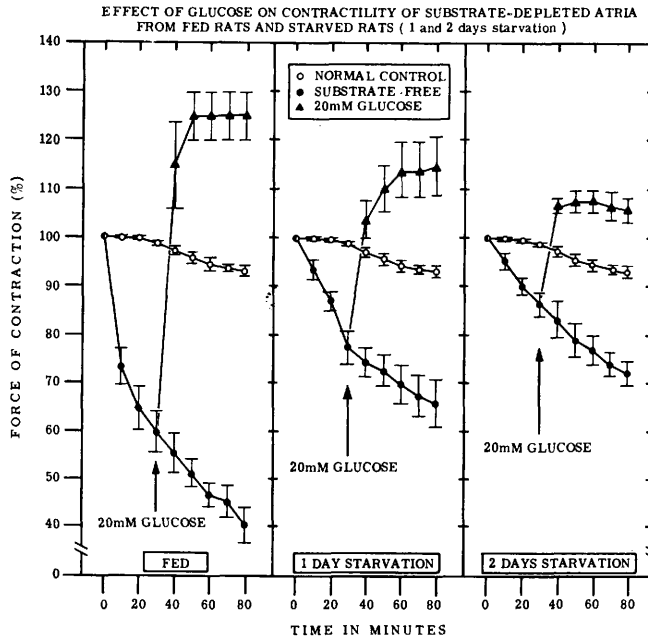


FIG. 3. Effect of glucose on force of contraction of substrate-free treated atria from fed and starved rats. Atria exposed to substrate-free medium at zero time (following a 1 hr equilibration in normal medium). Glucose added at 30 min.

medium than do those from fed rats. During the period of 6 days starvation, only 40% of the rats survived. However, the force of contraction of atria from rats treated for 6 days starvation was still higher than that from fed rats.

Effect of glucose on force of contraction of substrate-free treated atria from starved and fed rats. After 30 min incubation of atria from fed and starved rats in substrate-free medium, 20 mM glucose was added to each atria. Figure 3 shows that glucose produced a marked increase in force of contraction in all cases.

Discussion. The results indicate that atria from rats starved 1 to 6 days develop at least as much tension in glucose-containing medium as atria from fed rats, suggesting that prolonged starvation does not interfere with the functional integrity of the atrial musculature. Similar results were observed by Gimeno *et al.* (6, 7) with atria from 1- or 2-day starved rats. Also, atria from rats starved 1 to 6 days show a smaller decline in developed tension in the absence of exogenous sub-

strate than atria from fed rats. The latter point was demonstrated previously for atria from 24 hr starved rats (1, 6) and suggests that starvation increases the stores of readily available substrates for use in the contractile process. The slowest rate of decline of developed tension was seen in atria from rats starved for 2 days. This may indicate that 2 days of starvation is the optimum time period for accumulation of readily utilizable substrates by the atria and suggests a useful starvation period for future experiments.

Functional studies, with inhibitors of phosphofructokinase, suggest that endogenous substrates above and below the phosphofructokinase step in the glycolytic cycle may be used to support the developed tension of atria from 24 hr starved rats exposed to substrate-free medium (1). The nature of these endogenous substrates is likely to be lipid and glycogen (2, 8).

Although starvation results in an apparently greater utilization of lipid than carbohydrate by the heart (2, 9-16) this report demonstrates that the enzymes of glycolysis

are functional even after 2 days of starvation since glucose is able to produce a marked positive inotropic action in substrate-free treated atria from rats starved for this time period.

Summary. Starvation results in a marked loss of body weight in rats, *e.g.*, a 30% loss in 4 days after which the animals begin to die. By the sixth day only 5 of the 20 were still living. Despite these drastic effects on the rat as a whole, cardiac function, as determined by developed tension of isolated atria in glucose-containing medium, was as good or better than that from fed rats. When placed in substrate-free medium, atria from fed rats showed a marked decline in developed tension, *e.g.*, a 44% decline in 40 min. In contrast, the developed tension of atria from rats starved 1 to 6 days showed a smaller rate of decline with the least decline seen in atria from rats starved for 2 days. These results suggest (a) that prolonged starvation has no deleterious effect on cardiac function and (b) starvation increases the storage of readily metabolizable substrate useful for the functional activity of the atria.

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