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EFFECTS OF PROPRANOLOL ON TIME OF USEFUL FUNCTION (TUF) IN RATS--ETC(U)
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16. Abstract

To assess the effects of propranolol on tolerance to rapid decompression, a series of experiments was conducted measuring time of useful function (TUF) in rats exposed to a rapid decompression profile in an altitude chamber. In other experiments TUF was measured for rats exposed to an oxygen/nitrogen gas mixture which produced a hypoxic condition equivalent to that in the decompression experiments.

The findings were: (i) Rats become less tolerant to hypoxia of an onset rate comparable to that of rapid decompression when given propranolol, and this intolerance is further exacerbated by an increase in physical exertion. (ii) Younger animals are more susceptible to this type of hypoxia, but propranolol has no greater effect on hypoxia tolerance in younger animals. (iii) None of the reduced tolerance can be attributed to a shift in the oxyhemoglobin dissociation curve. In rats the curve is shifted slightly to the left, whereas in man there is a reported shift to the right.

Because propranolol impairs tolerance to hypoxia in experimental animals, it is important to assess its effects on human tolerance.

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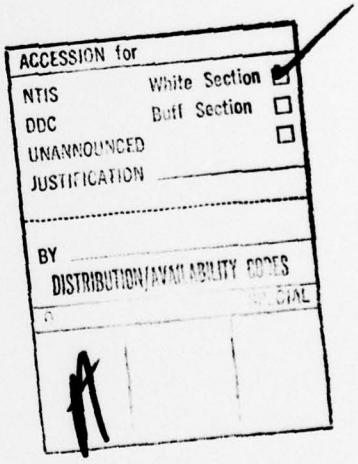

EFFECTS OF PROPRANOLOL ON TIME OF USEFUL FUNCTION (TUF) IN RATS

I. Introduction.

Propranolol, a β-adrenergic blocking agent, is widely used for control of cardiac arrhythmias, essential hypertension, and other medical conditions (3,5,6,13,21,25,26,28). Because it has minimal side effects (15,17,18), many requests are being received by the FAA's Aeromedical Certification Branch for approval of propranolol as a medication in the pilot group.

Several reports (1,11,12,14,16,19) have shown that propranolol shifts the oxyhemoglobin dissociation curve (ODC) to the right, thus reducing the oxygen transport capacity of hemoglobin. It has been suggested that this effect, combined with the β-adrenergic blocking effects on cardiovascular functions, might impair altitude tolerance, particularly tolerance to a rapid decompression.

To assess the effects of propranolol on tolerance to rapid decompression, a series of experiments was conducted on male Sprague-Dawley rats, first using the Civil Aeromedical Institute (CAMI) research altitude chamber for rapid decompression profiles and subsequently using an oxygen/nitrogen gas mixture to produce an equivalent hypoxic condition.

II. Methods.

Prior to the experiments, tests were made with untreated rats, following the decompression profile used in time of useful consciousness (TUC) studies of human subjects (7,8). This profile consists of: (i) rapid decompression from 6,500 ft to 34,000 ft (2,000 to 10,400 m) in 26 s; (ii) holding for 23 s at 34,000 ft (10,400 m); (iii) a descent at the rate of 5,000 ft/min (1,500 m/min). Because the rats did not lose useful function with this profile, it was decided to follow the profile only through the first minute of descent in the experiments on rats and to hold the chamber at 29,000 ft (8,800 m) until loss of useful function occurred.

To determine time of useful function (TUF), rats were placed inside a double-compartmented clear plastic wheel (16 in [40.6 cm] in diameter) covered with a plastic mesh (Figure 1). The wheel was rotated at 1 revolution per minute. Rotation was begun 1 min prior to decompression and continued until the rats were unable to walk within the rotating cage.

Two series of experiments were conducted using the decompression profile described above. In the first series, 60 young mature rats (274 to 462 g) were used. Twenty rats received intraperitoneal (IP) injections of normal

saline (control), 20 received 1.14 mg propranolol hydrochloride per kg of body weight (low dose), and the remaining 20 received 2.28 mg per kg of body weight (high dose). The high dose is equivalent to a single 160-mg dose for a 70-kg man, the maximum recommended dose (15) for treatment of hypertension (the maximum daily dose is 640 mg but divided into four equal doses). The low dose is half this amount. For the second series of experiments, smaller (248 to 321 g), less mature animals were used to determine if the effects were consistent in different age/weight groups. All IP injections were administered approximately 30 min before decompression.

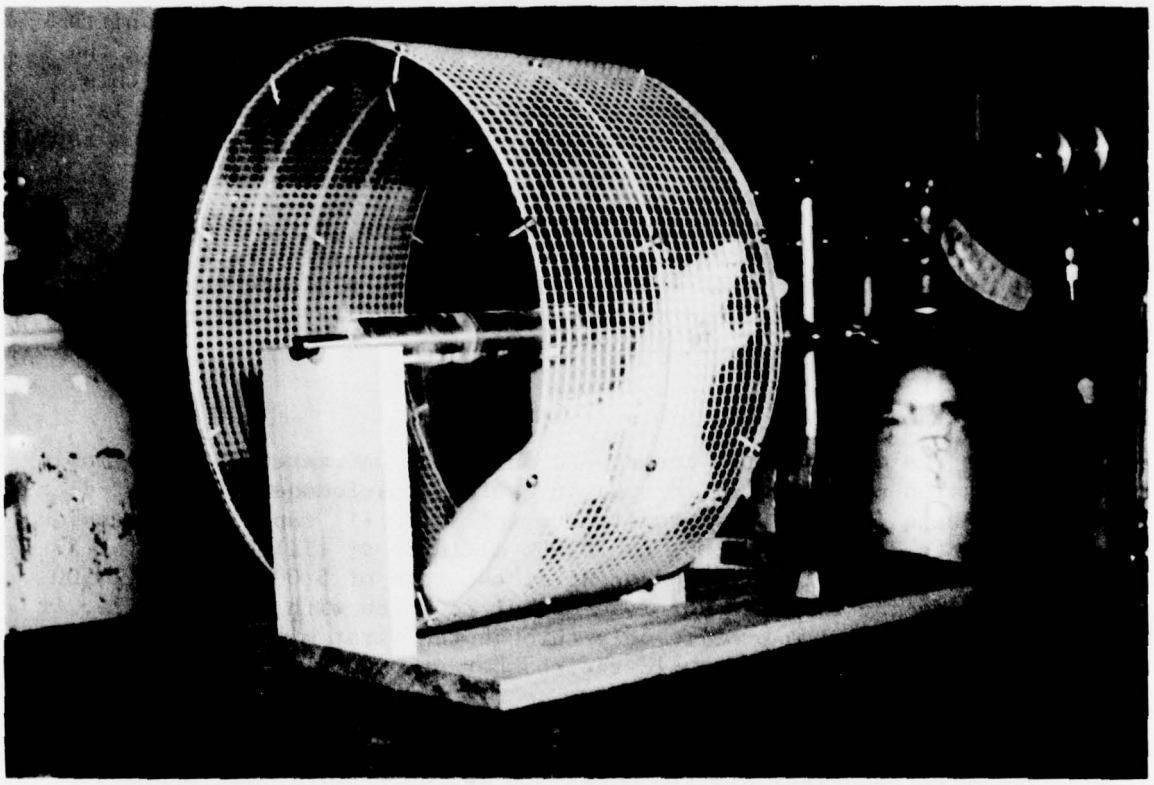

Figure 1.
Time of useful function (TUF) apparatus
used in decompression experiments.

In another series of experiments with 40 rats (20 saline treated and 20 receiving the high dose of propranolol), an oxygen/nitrogen gas mixture (5.206 percent O_2) was used to produce an equivalent hypoxic condition without hypobarism. Because of the large volume of the rotating wheel, it was not possible to replace the chamber air with the gas mixture in a time short enough to simulate the decompression profile. In order to maintain the profile, an alternate method was used to measure TUF. Rats were placed individually inside a clear plastic box (inside dimensions of 4 in by 4 in by 10 in: Figure 2), and this box was rotated 90^{o} laterally at approximately 2-s intervals. Time was measured from the beginning of the flushing period until the rat was no longer able to maintain an upright position when the box was rotated.

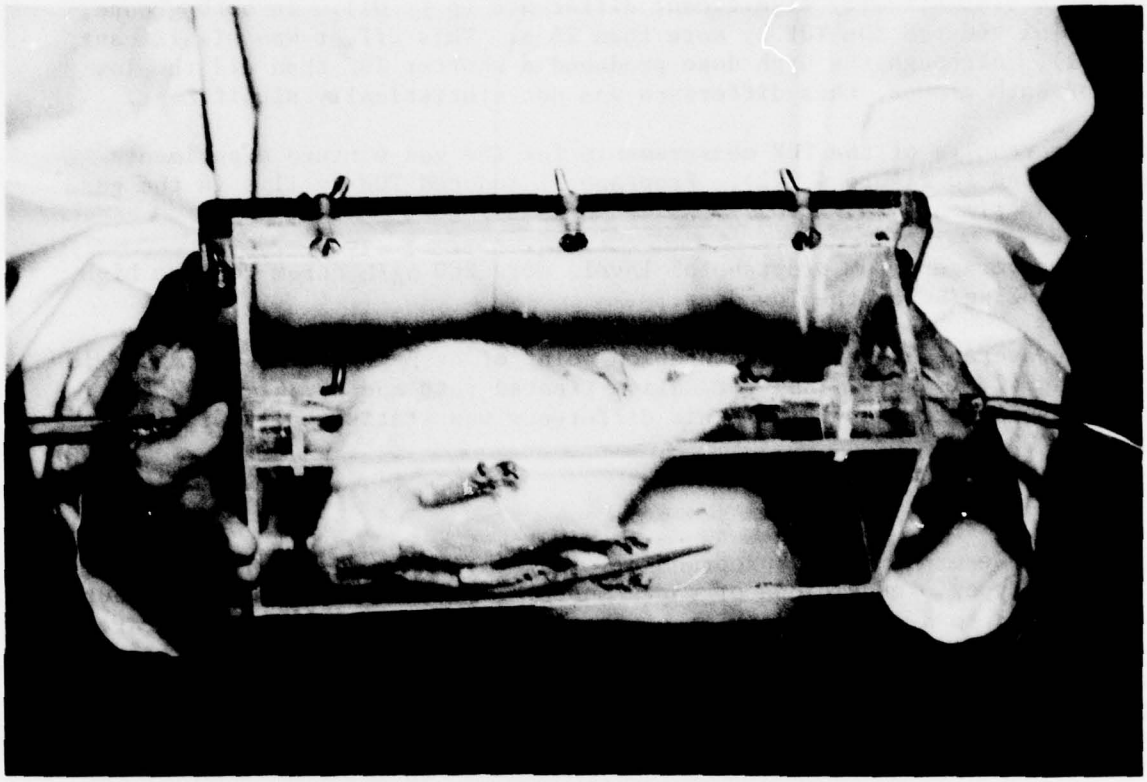

Figure 2.
Time of useful function (TUF) apparatus used in oxygen/nitrogen gas-mixture experiments.

At the end of each experiment the rats were anesthetized with diethyl ether, blood samples were drawn by means of cardiac puncture, and the animals were killed. Serum propranolol measurements were made by the method of Shand, Nuckolls, and Oates (20) as modified by Ayerst Laboratories. For the gas-mixture series of experiments the oxyhemoglobin dissociation curves of fresh samples of whole blood were measured (program A) on the Hem-O-Scan Oxygen Dissociation Analyzer (American Instrument Company, Silver Spring, MD).

III. Results.

The results of the TUF measurements for the decompression experiments are presented in Figure 3 (23). The TUF for the younger rats was 11-12 s shorter than for the older rats, regardless of the treatment administered. This was a statistically significant difference ($p \leq .01$). In both groups, propranolol reduced the TUF by more than 25 s. This effect was significant ($p \leq .01$). Although the high dose produced a shorter TUF than did the low dose for both groups, this difference was not statistically significant.

The results of the TUF measurements for the gas-mixture experiments are presented in Figure 4 (22). Propranolol reduced TUF by 11 s in the gas-mixture experiments ($p = 0.057$).

The average serum propranolol levels were 200 µg/L serum for the high dose and 162 µg/L for the low dose.

The average 50-percent saturation point of oxyhemoglobin, expressed in mm Hg, was 41.71 $\pm$ 2.92 (SD) for saline-treated rats and 39.36 $\pm$ 2.92 (SD) for propranolol-treated rats. This difference was statistically significant ($p \leq .05$)(23).

IV. Discussion.

In these experiments, propranolol significantly reduced the tolerance of rats to hypoxic conditions of rapid onset. This effect, however, cannot be attributed to a rightward shift of the ODC because the rats demonstrated a statistically significant shift to the left, although the change (2.35 mm Hg, a 5.6-percent decline) is probably not of great physiological significance. The rats, therefore, are not suitable models for evaluating the consequences of the rightward shift of the ODC that is reported to be produced by propranolol.

It is possible that the reduced tolerance to hypoxia is not solely a reflection of the β-adrenergic blocking effects of this drug. Bainbridge and Greenwood (4) reported a tranquilizing effect for propranolol that could not be attributed to a blockade of β-adrenergic receptors. In their study, the dextroisomer, which has practically no β-blocking properties, was as effective a tranquilizer as the racemate. In another study by Trivedi and Sharma (27) it was demonstrated that propranolol depresses the central

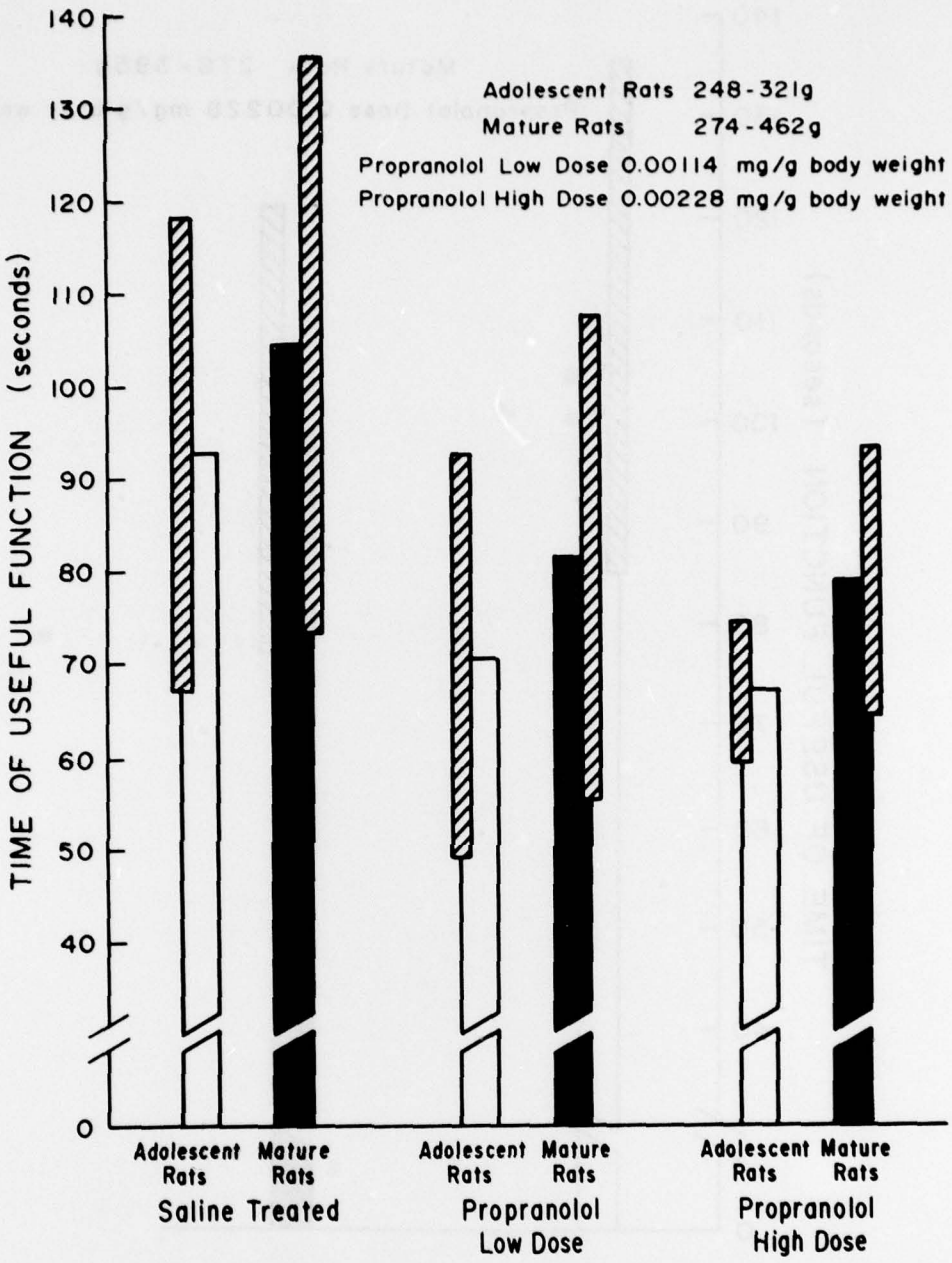

Figure 3.
Bargraph of mean and standard deviation for time of useful function (in sec) during decompression experiments. (N = 20, each group)

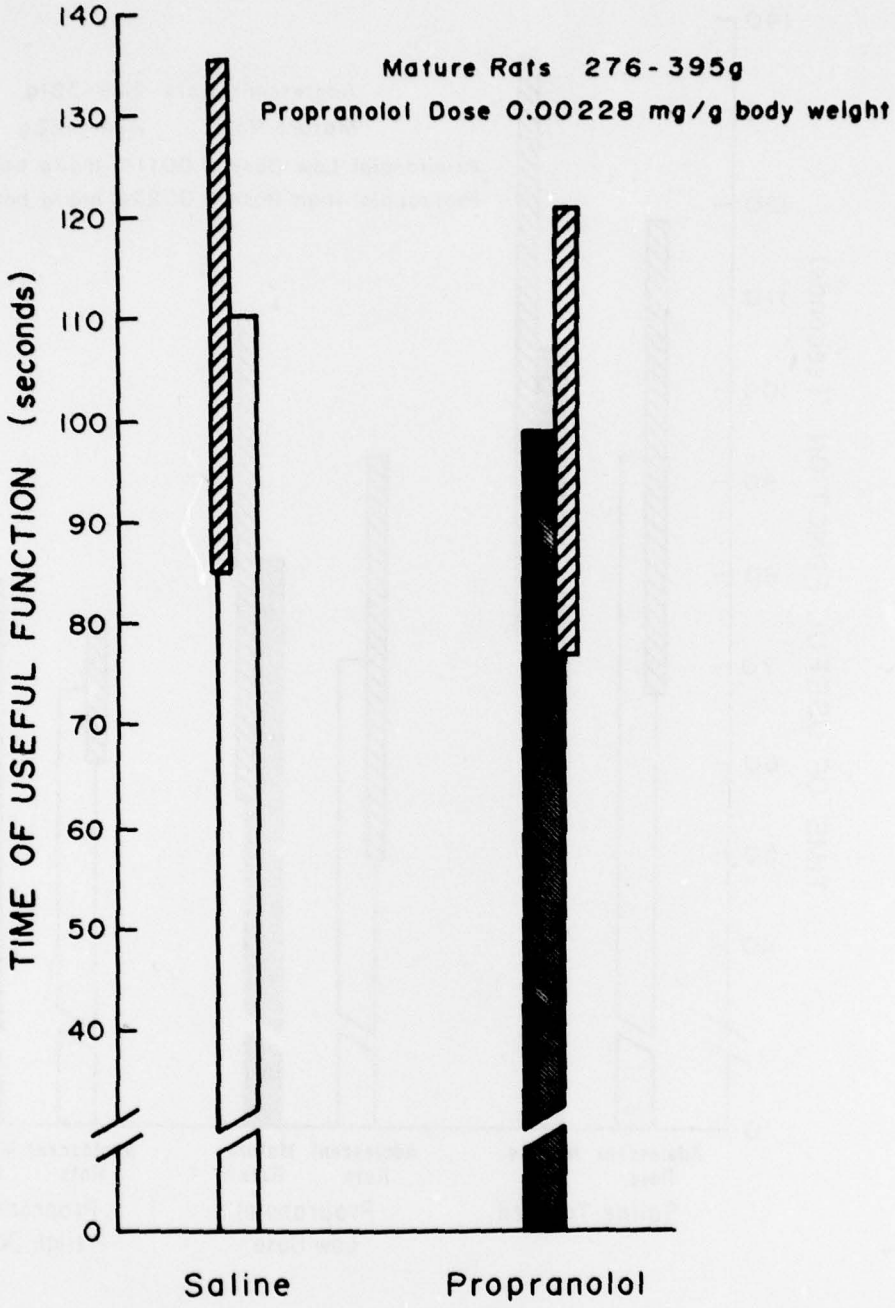

Figure 4.
Bargraph of mean and standard deviation for time of useful function (in sec) during gas-mixture experiments. (N = 20, each group)

nervous system, whereas another β blocker, dichloroisoprenaline, is an excitant. In view of these findings, the depressant effects of propranolol must be included in any attempt to explain its effects on the TUF.

Propranolol was not as effective in reducing the TUF when hypoxia was induced by a mixture of gases. However, this difference may not have been due to the difference in barometric pressure in the two experiments. It is more likely explained by the difference in physical activity required by the two methods of measuring TUF. The exercise level of the rats was considerably greater during the decompression experiments than during the gas-mixture experiments. This explanation is consistent with the report of Atkins and Horowitz (2) who found that blockade of autonomic control of the heart in dogs resulted in a diminished cardiac output during exercise by reducing heart rate and myocardial contractile force. This effect on cardiac output was not seen in the resting dog. Donald, Ferguson, and Milburn (9) reported the effects of propranolol on the racing time of normal and cardiac-denervated greyhounds. They found that the cardiostimulant action of sympathetic nerves and circulating catecholamines were both important to maximal performance. Ehrlich et al. (10) reported that the vasodilating action of β activity is essential for an increased coronary flow during exercise. Propranolol increased the arteriovenous oxygen difference and did not diminish the total oxygen consumption at rest and at the end of exercise. Snow and Summers (24) reported that propranolol and metroprolol, another β-blocking agent, decreased the racing performance of horses.

In light of the reports cited above, and our own observations regarding differences in the physical demands of the protocols, we conclude that the observed effects of propranolol were most likely due to inhibition of physiological adjustments to exercise and not due to any effects on the ODC. Furthermore, because both protocols involved some degree of exercise, we cannot rule out the possibility that this effect on physiological responses is the principal cause of the decrements in TUF observed in both experiments. It must be reiterated, however, that the ODC effects in man may be an important consideration. Therefore, a decision regarding this issue must await the design and execution of safe trials in human subjects or on more suitable animal models.

V. Conclusions.

Rats given propranolol are intolerant to hypoxia of an onset rate comparable to that of rapid decompression, and this intolerance is further exacerbated by an increase in physical exertion.

Younger animals are more susceptible to this type of hypoxia, but propranolol has no greater effect on hypoxia tolerance in younger animals.

None of the reduced tolerance can be attributed to a shift in the oxyhemoglobin dissociation curve. In rats the curve is shifted slightly to the left, whereas in man there is a reported shift to the right.

Because propranolol impairs tolerance to hypoxia in experimental animals, it is important to assess its effects on human tolerance.

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