# Lipemia-Induced Acceleration of Intravascular Clotting II. Effect of Hypoprothrombinemia.* (25263)

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Intravenous injection of a fat emulsion in anesthetized dogs is associated with accelerated clot formation in isolated vein segments (1). The present investigation was concerned with the question of whether such clot acceleration might also occur in dogs in which a hypoprothrombinemic state had been induced.

*Material and methods.* Mongrel dogs, weighing 13 to 22 kg, were given 25-50 mg of bishydroxycoumarin daily for 3-4 days until their one-stage "prothrombin" time(2) reached levels indicating less than 10% of prothrombin activity.† Under Pentobarbital anesthesia, the internal jugular and femoral veins were freed and isolated by clamps, and small segments of vein excised at regular intervals for determination of intravascular clotting time (ICT). This was the interval from moment of clamping veins of one side to removal of segment which contained the first grossly visible fibrin clot(1). Hemostasis during surgical procedure often was quite difficult because of extensive oozing of blood from tissues. Serum was collected before and after fat emulsion‡ (40 ml) was injected into peripheral vein, for estimation of optical density (at wave length 620 mμ) and of triglycerides(4).

*Results. Intravascular clotting time in fasting dogs.* In 11 hypoprothrombinemic dogs, ICT was measured in jugular and femoral veins of right side before fat emulsion was injected. These fasting values ranged 35-75 minutes (Table I); 2 control animals and 1 injected with the emulsion showed unduly low ICT's, because vein segments were exhausted before recognizable clot was observed. All dogs except one had plasma prothrombin concentrations less than 1%, the normal range of prothrombin time in dogs being 8-10 seconds. The longest ICT, 75 minutes, was in a dog with prothrombin time of 36 seconds, the longest prothrombin time, more than 100 seconds, was in a dog with ICT of only 55 minutes.

*Intravascular clotting time after injection of fat emulsion.* In 8 of 10 dogs, ICT determined in (left-sided) veins isolated 2 minutes after injection of fat emulsion was shorter than before injection by 5-35 minutes (Table I). One of the 2 remaining dogs showed the same ICT before and after injection; the lower post-emulsion value recorded for the other dog does not represent a reliable endpoint (see above). Shortening of ICT coincided with marked increase in lactescence, as well as in triglycerides of serum (Table I); the degree of shortening appeared to correspond roughly to the change in serum lactescence.§ In 2 other dogs, fat emulsion was injected before veins of either side were clamped (upper section, Table I). In one of these dogs, ICT was 10 minutes longer at time of decreasing lipemia, *i.e.*, about 35 minutes after injection, than at peak of lipemia,

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† This test chiefly reflects deficiency of factor VII (proconvertin) in plasma; after 3-4 days on above dosage, both prothrombin and Stuart factor are usually also depressed but to a lesser and unpredictable degree(3). The term hypoprothrombinemia refers to "prothrombin complex" rather than to prothrombin *per se*.

‡ This emulsion, containing 15% vegetable oil and 1.2% Soybean Phosphatide, furnished through courtesy of Don Baxter.

§ Neither parameter of lipemia was sufficiently accurate for analysis of correlation: Hemolysis incidental to collection of blood tended to increase optical density of serum, which was always determined on day of collection; some triglyceride values are probably erroneous because fat emulsion separated from serum after storage at 4°C for one or several days and did not mix well with shaking. Recovery experiments with emulsion added to serum were not very satisfactory. Hence, values for triglycerides and for lactescence listed in Table I will serve to illustrate direction of change of lipemia in each dog but do not lend themselves for precise computation of correlations.

TABLE I. Intravascular Clotting Time (ICT), Serum Triglycerides (TG) and Lactescence (L) before and after I. V. Injection of Fat Emulsion.

| Prothrombin time, sec. | Fasting ICT, min. | Fasting TG, mg/100 ml | Fasting L, % T | 2 min. after ICT, min. | 2 min. after TG, mg/100 ml | 2 min. after L, % T | 35-75 min. after ICT, min. | 35-75 min. after TG, mg/100 ml | 35-75 min. after L, % T |
|---|---|---|---|---|---|---|---|---|---|
| 45 | | | 87 | 20 | 84 | 36 | 30 | 54 | 52 |
| 21 | | | 63 | 25 | 471 | | 25 | 206 | |
| 26 | >35 | 81 | 66 | 30 | 125 | 31 | | 96 | 42 |
| 22 | 35 | | 91 | 35 | | 53 | | | 55 |
| 40 | >40 | 72 | 85 | 20 | 160 | 2 | | 128 | 73 |
| 31* | 60 | | 82 | | | | | | |
| 45 | 45 | 114 | 79 | >35 | 465 | 5 | | | |
| 50 | 65 | 64 | 79 | 55 | 556 | 5 | | 225 | 15 |
| 43 | 65 | | 86 | 45 | | 10 | | | 67 |
| 36 | 75 | 40 | 91 | 65 | 163 | 18 | | 105 | 34 |
| 36 | 55 | 75 | 83 | 35 | 103 | 13 | | 72 | 22 |
| 47 | 65 | 79 | 81 | 30 | 233 | 23 | | 134 | 61 |
| >100 | 55 | 83 | 78 | 35 | 211 | 35 | | 133 | 42 |

% T denotes % transmittance.

* Died after additional dose of pentobarbital before fat emulsion was inj.

as determined 2 minutes after injection. In the other dog, ICT was unchanged.

*Discussion.* ICT values in these severely hypoprothrombinemic dogs tended to be somewhat prolonged‖ when compared with those observed under the same conditions in dogs not pre-treated with bishydroxycoumarin. While untreated dogs usually yielded fasting values of 30-40 minutes(1), the present fasting range was 35-75 minutes and over-all range (for 25 estimations in 13 dogs), 25-75 minutes. All values were within the 20 to 90-minute period considered by Wessler as the normal range; this author had noted normal intravascular clot formation in 17 of 18 hypoprothrombinemic dogs, although slight retardation may have been overlooked(5).

ICT and one-stage prothrombin time showed poor correlation, a perhaps analogous observation that prothrombin time sometimes fails to provide a dependable measure of *in vivo* hypocoagulability or bleeding tendency (2,3). Whether or not ICT might correlate better with deficiency of individual plasma factors, which are coumarin-sensitive, such as prothrombin and Stuart factor, remains to be determined.

In spite of the apparent tendency to retardation of intravascular clot formation observed in coumarin-treated dogs, lipemia induced by administration of fat emulsion resulted in clot acceleration in most instances. While this acceleration might have to do with duration of surgical procedure and some blood loss or exhaustion, observations in the 2 dogs receiving fat emulsion at beginning of experiment seem to disprove this point: ICT was the same or longer on the "second" (left) side. Hence, ICT quite consistently tended to be shorter at height of lipemia, whether this occurred earlier or later in the surgical procedure.

It should be remembered that it may not be over-all "lipemia" but some ingredient of fat emulsion, presumably soybean phosphatide, which exerted the clot-promoting effect (6). Whatever the lipemic agent responsible for this effect, it has one property in common with the (unknown) thrombogenic substance contained in canine serum which, upon rapid intravenous infusion, causes an intravascular clot to form within 2 minutes(7). Neither effect is obviated by marked hypoprothrombinemia and bleeding tendency. This finding suggests that lipemia-induced clot acceleration is independent of that phase in the coagulation process which is reflected in the prothrombin time test, particularly factor VII.

*Summary and conclusions.* 1) Bishydroxycoumarin-induced hypoprothrombinemia may result in a slight delay of fibrin clot in isolated venous segments of anesthetized dogs. 2) The hemorrhagic state produced by the drug fails to prevent acceleration of intravas-

‖ The number of dogs used was considered too small for statistical evaluation.

cular clotting caused by intravenous infusion of fat emulsion. This clot acceleration, therefore, may not operate through the mechanism of prothrombin conversion. 3) Our experiments lend support to the concept that anticoagulation with coumarin-type drugs is not synonymous with antithrombotic effect.

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## Digital Pre- and Postcapillary Vasoconstriction and Vasodilatation Resembling Pre- and Postglomerular Arteriolar Function in Kidney.* (25264)

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Spontaneous variations in digital vascular volume have been described(1) quantitatively for man. They are generally classified into 5 types—pulse, respiratory, alpha, beta and gamma deflections. *Alpha deflections* have a mean frequency of 7.9/min. (range 2 to 14) and mean magnitude of 14.5 $mm^3/5$ cc of part (range 0.1 to 81). *Beta deflections* have a mean frequency of 1.3/min. (range 1 to 2) and mean magnitude of 30 $mm^3/5$ cc of part (range 5 to 60). *Gamma deflections* have a mean frequency of 4/hr (range 1 to 8) and mean magnitude of 150 $mm^3/5$ cc of part (range 50 to 350). Pulse deflections are superimposed upon alpha, beta and gamma deflections (Fig. 1). With marked vasoconstriction and marked vasodilatation the alpha, beta and gamma deflections are small to almost absent(1,2). The function of these spontaneous volume deflections has been a puzzle. With development of the rheoplethysmographic method for measuring simultaneously time courses of volumes and rates of digital inflow and outflow during a single pulse cycle(2,3), the significance of these spontaneous deflections is becoming apparent. *Theoretic considerations.* Large ascending and descending alpha, beta and gamma deflections are associated with large increases and decreases, respectively, in digital volume.

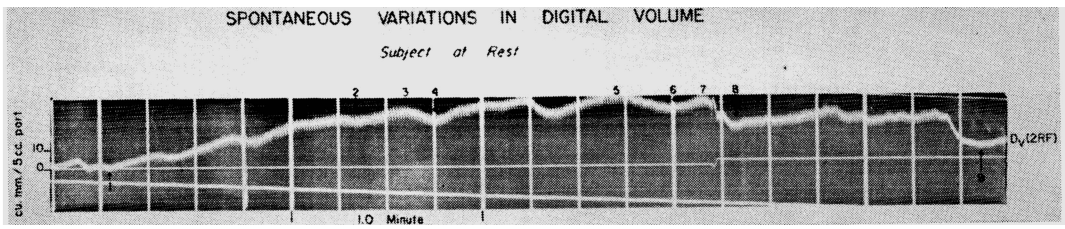


FIG. 1. A segment of a rheoplethysmogram recorded at slow camera speed showing variations in volume, $D_V$ (2RF), of the tip of right second finger (index finger). The pulse waves are superimposed upon alpha deflections (arrows 2 to 3 and 3 to 4, for example) which, in turn, are superimposed upon beta deflection (points 1 to 5 and 5 to 9).

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