Effects of Acute and Chronic Digoxin Administration in Dogs with Right-Sided Congestive Heart Failure Produced by Pulmonary Artery Constriction

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Acute and chronic responses to digoxin have been studied in dogs with cardiac failure secondary to constriction of the pulmonary artery. Cardiovascular and renal hemodynamic function improved and, frequently, a striking increase in sodium (Na) excretion resulted. The data suggest a direct myocardial action of digoxin and provide evidence of impaired myocardial function similar to that observed in patients with congestive heart failure.

IN the preceding paper¹ the state of the circulation in dogs with right heart failure secondary to controlled progressive constriction of the pulmonary artery was described. The present investigation was made in an attempt to induce a response to digoxin in dogs with pulmonary artery constriction. The observations provide additional evidence of a failing myocardium.

MATERIALS AND METHODS

The material for this study consisted of 7 female mongrel dogs in which the main pulmonary artery had been constricted progressively until cardiac failure developed. The method of producing cardiac failure was described in the preceding report.¹

The experimental design for the acute study consisted of observations for a 40 to 60 minute control period and for approximately 2 hours following intravenous administration of 1.0 to 1.2 mg. of digoxin. Observations were made on trained unanesthetized dogs in the postabsorptive state without hydration or saline load. Patency of an indwelling intracardiac catheter was maintained with 100 to 150 ml. of normal saline during the 2½ to 3 hour period; approximately the same quantity of blood was withdrawn for various analyses while the catheter was in place.

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The effects of chronic digoxin administration were studied in dogs 2-4; digitoxin was given to dog 1. Both digoxin and digitoxin were given 2 to 3 times daily; the doses of these drugs were increased progressively until Na excretion increased markedly or until vomiting precluded further increase in rate of administration. After a response was obtained, the drug was discontinued; later, therapy was re-instituted. All other experimental procedures and methods have been described previously.¹²

RESULTS

Effects of Acute Digoxin Administration in Dogs with Cardiac Failure: The acute response to 1.0 to 1.2 mg. of intravenous digoxin was observed in 7 dogs at the onset of right heart failure secondary to pulmonary artery constriction. Before receiving digoxin, all animals showed a low cardiac output, elevated right atrial pressure (RAP), high right ventricular systolic pressure, slight depression in arterial pressure, normal or depressed renal hemodynamic function, and a very low rate of Na excretion; also, ascites was present in all dogs. Following digoxin, a decrease in RAP was observed within 15 minutes (figs. 1 to 3). The fall in RAP occurred in every instance; the average decrease for the 7 dogs was from 211 to 162 mm. water. Cardiac output increased 11-70 per cent in 5 of the 7 animals (see figs. 1 to 3); in the other two dogs a slight drop occurred. Since heart rate decreased slightly or remained unaltered, an increase in cardiac
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Output was affected by increased stroke volume. Femoral arterial pressure remained unchanged throughout the 2 hour observation period in all 7 dogs except for a slight elevation in mean pressure in dog 4 (fig. 3). Total peripheral resistance was reduced in the 5 animals showing increased cardiac output. Right ventricular systolic pressure increased from an average value for the 7 dogs of 83 mm. Hg to 100 mm. Hg; in dog 2 (fig. 2) a 28 per cent increase resulted and in dog 4 (fig. 3) an elevation of 29 per cent occurred.

A striking increase in renal Na excretion occurred in 4 of the 7 animals (dogs 2, 5, 6 and 7; figs. 2 and 4) and increased water excretion always accompanied increased Na output. An increase in glomerular filtration rate (GFR) and effective renal plasma flow (RPF) resulted in every dog. In some instances the increase was evident during the first post-digoxin period (fig. 3), while in other dogs renal hemodynamic function remained unchanged until the third period following digoxin (fig. 2). The maximal level of GFR and RPF usually occurred during the last post-digoxin period; GFR increased from 50 to 63 cc. per min. whereas RPF increased from 111 to 151 cc. per min. (mean values for 7 dogs).

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Fig. 1. Effect of intravenous (i.v.) digoxin on cardiac output (CO) in L./min., right atrial pressure (RAP) in mm. water, glomerular filtration rate (CCR) in cc./min. and urinary Na excretion (ENa) in μEq./min. in a dog with right heart failure. The broken horizontal line represents the average of two control values for CCR. Values for RAP in this figure and in figures 2, 3 and 4 were obtained with a water manometer.

Fig. 2. Changes in cardiovascular hemodynamics and kidney function after intravenous injection of 1.0 mg. of digoxin in a dog with right heart failure. Abbreviations are for right ventricular systolic pressure (RVSP) in mm. Hg, cardiac output (CO) in L./min., total peripheral resistance (TPR) in dynes-sec.-cm.−², femoral arterial systolic (—●—), mean (—△—) and diastolic (—⊙—) pressures (BP) in mm. Hg, right atrial pressure (RAP) in mm. water, glomerular filtration rate (CCR) in cc./min. and renal Na excretion (ENa) in μEq./min. The broken horizontal line indicates the average of two control determinations of CCR. RVSP is plotted as a solid bar from a line representing the average control value.
Dogs with Cardiac Failure: The typical chronic response to digoxin is shown for dog 3 (fig. 5). After 10 days of control observations during cardiac failure, 1.0 mg. of digoxin was given intravenously; Na excretion remained low. Thereafter, 0.5–1.0 mg. per day of digoxin was administered orally. After 7 days of digoxin therapy, measurements showed a striking increase in right ventricular systolic pressure and cardiac output, an elevation in arterial pressure, and a slight increment in GFR; however, RAP was not reduced and Na excretion remained low. On the following day (after 8 days of therapy) Na excretion began to increase and a natriuresis ensued. By the twelfth and last day of the first course of digoxin, RAP had declined to 135 mm. water and a further slight elevation in cardiac out-

Fig. 3. Response to intravenous digoxin in a dog with right heart failure. See figure 2 for abbreviations; effective renal plasma flow in cc./min. is indicated by Ccr.

Fig. 4. Relation of renal Na excretion in µEq./min. (ordinate) to right atrial pressure in mm. water (abscissa) before (open symbols) and after (solid symbols) intravenous administration of digoxin to 7 dogs with right-sided congestive failure.

Fig. 5. Chronic response to digoxin administration in a dog (15.9 kg.) with right-sided congestive failure. See Fig. 2 for abbreviations; renal Na excretion is expressed in m.Eq./day. 1.0 mg. of intravenous digoxin (shown by solid bar) was given at beginning of each course of therapy; thereafter, digoxin was administered orally (dotted area). Scale at left shows mg./day of digoxin administered.
put and GFR was demonstrable. To exclude the possibility that improvement was spontaneous, digoxin was discontinued. Sodium retention promptly ensued, RAP increased and a reduction in right ventricular systolic pressure, cardiac output, arterial pressure and GFR resulted. Reinstiution of digoxin therapy effected improvement in cardiovascular and renal hemodynamic function and Na balance became negative. Similar findings were obtained in the other 2 animals which were given digoxin except that improvement in dog 4 was not sufficient to effect a natriuresis; a response to digitoxin occurred in dog 1.

**Discussion**

The data demonstrate a response to digoxin in dogs with right heart failure secondary to pulmonary artery constriction. Cardiovascular and renal hemodynamic function improved and a striking natriuresis was frequently observed. The increase in right ventricular systolic pressure suggests that digoxin exerted a direct effect on the right ventricular myocardium. The elevation in cardiac output is in contrast with the decreased output of the heart which occurred following administration of digitalis to normal dogs. In studies with intravenous digoxin in patients with cor pulmonale, only cases with cardiac decompensation showed a response in cardiovascular hemodynamics. It appears, therefore, that improvement in cardiovascular function with digoxin results only in the presence of myocardial depression. Consequently, the present observations provide evidence of impaired myocardial function in dogs with a congestive syndrome and chronic fluid retention secondary to pulmonary artery constriction.

The acute changes in cardiovascular hemodynamics observed in the present study were very similar qualitatively to those reported during the acute response to intravenous digoxin in patients with congestive heart failure secondary to cor pulmonale. However, the dose of digoxin per unit body weight required to produce the acute response in dogs was 3 to 5 times that used in man. Also, the daily maintenance dose of digoxin and digitoxin per Kg, of body weight was considerably greater.

The mechanism of the natriuresis which accompanies the administration of digoxin is not understood. Eichna and associates made extensive measurements in patients with cardiac decompensation but these workers were unable to prove a causal relationship between a specific change in cardiovascular or renal hemodynamic function and Na excretion. During the present observations, the increase in Na excretion occurred in dogs showing the most improvement in cardiovascular function. RAP fell to a lower level and the increase in cardiac output was larger in the animals in which Na excretion increased. The data from the acute study suggest that increased GFR was not of primary importance in the natriuresis because the largest relative increases (dogs 1 and 4) and the highest level of GFR (dog 1) occurred in dogs in which Na excretion remained low.

**Summary and Conclusions**

The acute and chronic effects of digoxin on cardiovascular and renal hemodynamic function and Na excretion have been studied in dogs with right heart failure produced by pulmonary artery constriction. The response included an increase in right ventricular systolic pressure and cardiac output, a fall in RAP and total peripheral resistance, an elevation in GFR and RPF, and a striking increase in Na and water excretion. The data suggest an effect on the right ventricular myocardium and provide evidence of myocardial depression in dogs with pulmonary artery constriction.

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**REFERENCES**

Evaluation of the Glass or Wax Spherule Technic for Studying A-V Anastomoses

By use of the method of injecting glass or wax spherules into an arterial branch, it has been concluded that 40 micra or larger A-V anastomoses occur almost universally.

Recent studies at the Medical Research Institute of the Max-Planck Gesellschaft in Göttingen indicate that, in dogs, denervation of a leg facilitates passage of wax spherules 32 and 40 micra in size, but this facilitation occurs largely in vessels of the foot.

More important, however, they analyze some of the possible pitfalls of the wax spherule technic. The difficulties are partly technical and partly biologic: the number of injected spherules cannot be accurately determined by the best technic; nor can the number passing through the peripheral arterial area be determined exactly by sampling blood from a single vein. Some estimate of the aliquot venous drainage can be obtained by concurrent use of Evans Blue. However, a lack of temperature control of the perfusate, as well as of the room, and uncontrollable temperature changes of the perfused territories due to variations in anesthesia—which has subtle effects on temperature regulation—may alter the size of arterioles and/or A-V anastomosis. It was often found that fewer spherules of larger size pass into the venous circulation on a second injection. Since the spherules used (up to 40 micra) were too small to cause embolization, and since the volume flow per minute had not changed, it was suspected that the spherules act as foreign bodies which induce constriction of A-V passages. The possibility also exists that spherules are not always distributed in the same proportion to the leg regions drained by a sampling vein. Finally, the possibility exists that spherules larger than the diameter of vessels may be pushed through distended elastic vessels.

For details and other references see J. Piiper and W. Schoedel, Arch. f. d. ges. Physiol. 258: 489, 1951.
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