THE EFFECT OF DIGOXIN ON THE RIGHT VENTRICULAR PRESSURE IN HYPERTENSIVE AND ISCHÆMIC HEART FAILURE

BY

R. I. S. BAYLISS, M. J. ETHERIDGE, A. L. HYMAN,* H. G. KELLY,†
J. McMICHAEL, AND E. A. S. REID‡

From the Postgraduate Medical School of London

Received April 3, 1950

In the early period of cardiac catheterization there was little inclination to pass the catheter tip beyond the right atrium, and therefore only right atrial pressures and cardiac output measurements were available (McMichael and Sharpey-Schafer, 1944a; Stead *et al.*, 1948). The essential findings in this and Stead's laboratory were that digoxin or lanatoside C reduced the right atrial pressure early, and usually increased the cardiac output. Both groups, however, observed a few cases in which the right atrial pressure fell without any significant change in cardiac output. This pressure-reducing action was frequent enough to suggest that it might play a primary role; and this view was supported by (1) simultaneous observations that venesection might cause an increase in cardiac output of the same order as that produced by digoxin, and by (2) published work suggesting that digitalis reduced venous pressure in normal animals (Dock and Tainter, 1930) and in man (Rytand, 1933). This conception had the additional attraction of offering a possible explanation for some of the failures of digitalis therapy in certain instances of "high output heart failure" in which increased venous pressure was perhaps compensatory in nature.

Further observations, however, have compelled revision of this view. On making detailed comparisons it was realized that the heart did more work after digoxin than after venesection (Howarth, McMichael and Sharpey-Schafer, 1946). Bloomfield *et al.* (1948) showed that in a wide variety of patients with heart failure ouabain had a direct stimulating action on the myocardium—a result that has been confirmed by Ahmed *et al.* (1950). In selected groups of cases it has been shown on the one hand that digoxin can increase the cardiac output in left ventricular failure without there being necessarily a concomitant reduction in venous pressure (Harvey *et al.*, 1949), and on the other hand that the venous pressure may fall without there being any measurable increase in output (McMichael and Sharpey-Schafer, 1944a). Deductions from the results of earlier observations were based on Wiggers' interpretation of Starling's law that small changes in filling pressure of the heart were of paramount importance in determining the strength of the cardiac contraction. Such an assumption cannot be accepted unreservedly. Warren *et al.* (1948) have shown that the output of the normal human heart is subject to controls more complex than simple government by Starling's law. Thus the significance of small changes in filling pressure of the order of 1–2 cm. saline becomes more difficult to assess. Experience has also made us aware of the random error in measurement of cardiac output by the technique of catheterization, the great variety of hæmodynamic changes in different types and grades of heart failure, and the varied responses to digitalization.

Unanswered problems and conflicting observations still abound. Harvey *et al.* (1949) have found in left ventricular failure without systemic venous congestion that digoxin produced a fall

* Fellow, National Heart Institute, United States of America.

† Nuffield Foundation Travelling Fellow in Medicine.

‡ Caverhill Fellow in Medicine, McGill University.

in the systolic pressure without any fall in the diastolic pressure in the right ventricle, whereas Lagerlof and Werko (1949) often observed both an increase and decrease in systolic and diastolic right ventricular pressures after lanatoside C. The fall in right atrial pressure that follows digoxin and lanatoside C, and may precede and be independent of changes in cardiac output, still demands an explanation. It was decided, therefore, to make further observations on the action of digoxin using optical records of the right ventricular pressures as an aid to interpretation.

METHODS

The cardiac output was measured by the Fick principle using the same techniques as before (McMichael and Sharpey-Schafer, 1944b) with the following additional precautions: (1) the Haldane blood-gas apparatus was immersed in water to eliminate any temperature changes (Douglas and Priestley, 1948); (2) blood samples were stored under oxygen-free paraffin and quickly cooled in ice if there was to be any delay in their analysis; and (3) two or three control samples were always taken under resting conditions. The coefficient of variation of the arteriovenous oxygen difference is ± 3.5 per cent, and of the oxygen uptake ± 5 per cent (Pugh and Wyndham, 1950). Assuming the variances to be additive, the coefficient of variation of a single determination of cardiac output is ± 6.0 per cent. When two or three estimations are made at or near the critical periods of the observation, this error may of course be reduced, and by studying a number of cases trends of behaviour may be established.

Respirations were recorded from a thermocouple inside a short length of glass tubing which was inserted into the nose. An electrocardiogram, usually lead II or III, was also recorded.

Pressure measurements. The fluctuating pressures in the right ventricle may be recorded by a technique similar to that used by Wiggers (1928) in animals. In man difficulties arise because the long intracardiac catheter damps down the frequency response of any recording device. We have used the strain gauge (Lambert and Jones, 1948) which is sturdy and can be operated in conjunction with a high-frequency mirror galvanometer without any intermediate amplification. Two Statham strain gauges have been used—one (0–15 lb./sq. in.) for recording intra-arterial pressures through an indwelling needle in the brachial artery, and the other (0–4 lb./sq. in.) for intraventricular pressures. In some cases the 0–15 lb./sq. in. gauge has been used for measuring intraventricular pressures. The instruments' natural frequency was of the order of 100 cycles a second, but this was damped down to a frequency of 17–20 cycles a second by the catheter. A suitable needle was interposed between the catheter and the gauge to eliminate overswing. According to Wiggers the most rapid components in a harmonic analysis of the intraventricular pressure curve may be 25 cycles a second. We, therefore, make no claim that our pressure records give the exact shape of the intraventricular pressure curve. We believe, however, that they are sufficiently accurate during the slower pressure fluctuations that take place in diastole and during the short period of sustained pressure usually inscribed in systole to indicate the ventricular systolic and diastolic pressures. Fig. 1 and 2 show the behaviour of the strain gauge under various conditions of test.

In analysing the pressure tracings from the right ventricle, we have followed the technique of Bloomfield *et al.* (1946), and measured the systolic pressure (P_s) and the end diastolic pressure (P_{d_2}) just before ventricular systole. The intraventricular pressures rise and fall with respiration, and therefore the systolic and diastolic pressures during at least one complete respiratory cycle have been measured and the results averaged for the recording of P_s and P_{d_2} .

It will be noted from Fig. 3 that the systolic pressure in the right ventricle may be regarded as the same as the pulmonary artery systolic pressure. The end diastolic pressure in the ventricle indicates the tension within that chamber immediately before the myocardium begins to contract.

P_{d_2} follows a small peak of pressure during ventricular diastole coincident with auricular systole. In most instances, therefore, P_{d_2} is identical with the pressure in the auricle at this moment (Fig. 4). It is a better measure of diastolic filling pressure of the ventricle than mean auricular

pressure. In most cases changes in Pd_2 will be paralleled by changes in mean auricular pressure; exceptions arise in such conditions as tricuspid valve disease.

Mean intraventricular pressures were recorded by the usual water manometer. Changes in the mean pressure followed closely those in the mean pressure calculated by planimetric integration of the optical records. Since the shape of the ventricular pressure curves may not be strictly accurate,

FIG. 1.—Response of strain-gauge (0–4 lb./sq. in.) to a square pressure. (A) Showing overswing. (B) Satisfactory damping by introducing a 22-gauge needle between the catheter and strain-gauge.

planimetric means may be liable to slight errors. Great care is necessary in order to observe the mean intraventricular pressure with a water manometer. Obstruction of the catheter tip by contact with the moving ventricular wall at any phase of the cardiac cycle can interfere with the proper recording of the mean pressure. Special attention was given to the character of the pulsations in

FIG. 2.—Comparison of arterial pressure recordings with and without a cardiac catheter between the indwelling needle and the strain gauge (0–15 lb./sq. in.). Records taken (A) with the gauge attached directly to the arterial needle, and (B) one minute later with a catheter between the needle and gauge. Note that the pulse wave contours, and the systolic and diastolic pressures are not significantly different. (The oscillating line is an artefact from a second galvanometer.)

the water manometer, and if the fluid failed to rise and fall freely or if there was any suggestion of a sudden jerky arrest of movement, the position of the catheter was adjusted to ensure "free" movements.

Digoxin was given in doses of 1.0–1.5 mg. depending on the size of the patient. After the drug was given observations were continued for about one hour. Significant reactions were nearly always obtained within that time, but it is not claimed that these represent the full and ultimate response to maintained digitalis therapy.

FIG. 3.—Record from (A) pulmonary artery, and (B) right ventricle. From above downwards—respirations (upward deflection on inspiration), pressure in mm. Hg, and electrocardiogram. Note that the systolic pressures in the pulmonary artery and right ventricle are the same.

FIG. 4.—Record from (A) right atrium, and (B) right ventricle in a case of constrictive pericarditis. From above downwards—respirations and pressure tracing in mm. Hg. Note that the peak of pressure in ventricular diastole and the pressure of the *a* wave in the right atrium are identical (22 mm. Hg) as there are different calibrations in the two records.

RESULTS

Significance of intracardiac pressures. The normal systolic pressure in the right ventricle ranges from 18–30 mm. Hg. while the end diastolic pressure fluctuates around a level opposite the centre of the heart (in a plane 5 cm. behind the sternal angle), the level that we have adopted as our reference point for all pressure measurements. A diastolic pressure greater than 4 mm. Hg. is probably abnormal. Our experience confirms that of Bloomfield *et al.* (1946) that very great rises in right

heart pressure may occur in various forms of left heart failure. We have encountered pressures as high as 90 mm. Hg systolic in failing mitral stenosis and also in hypertensive left ventricular failure. These high pulmonary artery pressures accompany left heart failure and to some extent parallel its severity at the time of observation. With clinical improvement, the systolic pressure in the pulmonary artery (and therefore in the right ventricle) falls dramatically. The high pressures are probably initiated by an increase in the pulmonary venous pressure determining an increased vascular pressure throughout the lungs.

Changes in these patients with digoxin. Two patients (Nos. 1 and 2) showed a significant increase in cardiac output without any significant alteration in the right ventricular pressures.

Ten patients showed a fall in right ventricular systolic and end diastolic pressures (Nos. 3–12). In four of these (Nos. 3, 4, 7, 12) there was an associated rise in cardiac output, a type of response well-illustrated in Fig. 5 (Case No. 3), where the cardiac output rose from 2.9 to 3.8 litres a minute, while the right ventricular systolic and diastolic pressures fell. In the other six (Nos. 5, 6, 8–11) the cardiac output did not change significantly despite the fall in right ventricular pressures: the response in Case No. 11 is included in this group despite a rise of 8 mm. Hg in systolic pressure because there was a fall in end diastolic pressure of 5 mm. Hg and the planimetric mean pressure fell from 35 to 27 mm. Hg.

FIG. 5.—Case No. 3. (A) Before digoxin. Right ventricular pressures in mm. Hg: Ps, 40; Pd₂, 1. Cardiac output 2.9 l./min. (B) 18 minutes after 1.5 mg. digoxin. Ps, 21; Pd₂, -5. Cardiac output 3.8 l./min. Note auricular premature beats in tracing (B), and marked respiratory fluctuations.

Perhaps the closest approximation to the grossly enfeebled heart of the pharmacological laboratory is Case No. 9 (Fig. 6), a known hypertensive whose condition was deteriorating and whose arterial blood pressure had fallen from a previous figure of 180/100 to 85/53 when the observations were made. The circulatory responses to 1.0 mg. digoxin were dramatic. The low arterial pressure rose, while the high systolic and diastolic pressures in the right ventricle fell to low normal levels. The reduction in end diastolic pressure in the ventricle signifies a fall in atrial pressure and relief of venous congestion; the reduction of right ventricle systolic pressure, and therefore of systolic pulmonary artery pressure, probably indicates a fall in the vascular pressures throughout the lungs. The cardiac output remained unchanged at 4 litres a minute, but with the raised arterial pressure the work of the left ventricle was clearly increased. Fig. 7 (Case No. 6) shows a similar response in a patient with hypertensive heart disease.

A rise in arterial pressure of more than 10 mm. Hg, systolic or diastolic, is a common accompaniment of full intravenous digoxin dosage, and occurred in eight (Nos. 1, 7, 9, 10, 11, 13–15) out of 15 patients. It is a rapid reaction, which comes on soon after digitalization and usually passes off within half an hour. In three patients (Nos. 13–15, Table II) the rise in blood

FIG. 6.—Case No. 9. Brachial artery and right ventricular pressures. From above downwards—respirations, arterial record, right ventricular record, electrocardiogram. (A) Before digoxin. Arterial pressure 85/53. Right ventricular pressure: Ps, 55; Pd₂, 13. Cardiac output 4 l./min. (B) 12 minutes after 1.0 mg. digoxin. Arterial pressure 139/100. Ps, 31; Pd₂, 9. Cardiac output 4 l./min. (C) 28 minutes after digoxin. Arterial pressure 146/87. Ps, 17; Pd₂, 1. Cardiac output 4 l./min. (D) 39 minutes after digoxin. Arterial pressure 128/78. Ps, 9; Pd₂, -1. Cardiac output 4 l./min.

pressure was particularly marked; it persisted throughout the period of observation and was associated with a rise in the right ventricular pressures. In two of these three the cardiac output fell and in the third it remained unchanged. All became increasingly dyspnoeic and orthopnoeic, and one (No. 13) developed frank pulmonary oedema. During the control period her diastolic pressure in the right ventricle was normal, but her systolic pressure was 31 mm. Hg (Fig. 8). The cardiac output was 3.2 litres a minute, and the arterial pressure 154/108. After intravenous digoxin the arterial pressure rose to 190/?, the pressure in the right ventricle climbed steadily to 65/7, and the cardiac output fell to 2.1 litres a minute. This exemplifies the induction of left ventricular failure by full intravenous digoxin dosage.

TABLE I
RIGHT VENTRICULAR PRESSURE AND CARDIAC OUTPUT IN HYPERTENSIVE AND ISCHEMIC HEART FAILURE

Case No.	Age	Sex	Diagnosis*	Time after Digoxin	Right ventricular pressure mm. Hg.		Brachial artery pressure		Cardiac output l./min.	Rate	Clinical notes
					Ps	Pd ₂	S	D			
1	60	F	H.H.D.	Control 27 min.	26 24	3 3	164 182	106 102	2.8 3.4	68 68	Exertional dyspnoea for 1 year; two attacks of paroxysmal nocturnal dyspnoea.
2	53	F	H.H.D.	Control 18 min. 32 min.	68 70 67	7 6 10	230 230 230	118 114 116	2.9 2.8 3.5	87 92 98	Exertional dyspnoea and attacks of paroxysmal nocturnal dyspnoea.
3	63	M	I.H.D.	Control 18 min.	40 21	1 -5	135 135	98 96	2.9 3.8	105 102	Exertional dyspnoea for 8 years; peripheral oedema; pulmonary congestion; hepatic enlargement; left pleural effusion.
4	68	M	H.H.D.	Control 52 min. 64 min.	67 72 57	13 7 6	165 214 208	125 116 110	2.0 2.4 2.7	88 72 76	Marked peripheral oedema; hepatic enlargement; right pleural effusion.
5	60	M	I.H.D.	Control 24 min. 40 min.	59 34 27	7 -2 2	134 146 144	82 74 76	3.3 3.5 3.4	72 72 72	Angina pectoris; myocardial infarct; congested neck veins.
6	64	M	H.H.D.	Control 20 min. 29 min.	43 32 26	1 -1 -2	185 194 194	124 122 122	4.0 3.8 3.8	98 72 72	Exertional dyspnoea; attacks of paroxysmal nocturnal dyspnoea.
7	55	F	H.H.D.	Control 18 min. 22 min.	63 71 59	18 11 11	158 192 192	118 126 122	2.6 2.9 3.1	84 84 82	Paroxysmal nocturnal dyspnoea and orthopnoea for 11 months; peripheral oedema; hepatic enlargement.
8	52	F	H.H.D.	Control 34 min.	45 36	7 4	260 240	170 148	3.4 3.4	108 88	Exertional dyspnoea; presystolic gallop rhythm.
9	82	M	H.H.D.	Control 12 min. 28 min. 39 min.	55 31 17 9	13 9 1 -1	85 139 146 128	53 100 87 78	4.0 4.0 4.0 4.0	115 115 114 116	Peripheral oedema; right pleural effusion.
10	63	M	H.H.D.	Control 20 min. 47 min.	32 25 15	2 2 -1	181 183 200	118 119 123	3.4 3.0 3.1	85 90 90	Attacks of paroxysmal nocturnal dyspnoea.
11	87	F	H.H.D. I.H.D.	Control 14 min. 60 min.	65 76 73	21 26 16	165 192 195	94 98 103	1.6 1.6 1.7	88 88 88	Exertional dyspnoea for 1 year; peripheral oedema; hepatic enlargement.
12	71	M	H.H.D.	Control 31 min. 58 min.	76 42 38	13 -4 -4	— — —	— — —	4.8 5.6 5.5	88 88 88	Exertional dyspnoea; peripheral oedema and orthopnoea.

* H.H.D.—hypertensive heart disease. I.H.D.—ischemic heart disease.

TABLE II
DEVELOPMENT OF PULMONARY CONGESTION AFTER DIGOXIN

Case No.	Age	Sex	Diagnosis*	Time after Digoxin	Right ventricular pressure mm. Hg.			Brachial artery pressure		Cardiac output l./min.	Rate	Clinical notes
					Ps	Pd ₂		S	D			
13	75	F	H.H.D. I.H.D.	Control 18 mins. 27 mins.	31	-1		154	108	3.2	86	Anginal pain; exertional dyspnoea; minimal peripheral oedema. Developed dyspnoea.
					55	3		180	114	—	88	
					65	7		190	—	2.1	96	
14	63	M	H.H.D.	Control 16 mins. 23 mins.	40	3		245	119	6.6	100	Exertional dyspnoea; orthopnoea; chronic bronchitis.
					37	3		257	121	5.2	100	
					42	12		274	128	5.0	112	
15	72	M	I.H.D.	Control 30 mins.	53	7		154	76	5.2	80	Exertional dyspnoea; paroxysmal nocturnal dyspnoea. Peripheral oedema.
					54	10		175	85	5.2	80	

* H.H.D.—hypertensive heart disease. I.H.D.—ischaemic heart disease.

FIG. 7.—Case No. 6. (A) Before digoxin. Right ventricular pressures in mm. Hg. Ps, 43; Pd₂, 1. Cardiac output 4 l./min. (B) 29 minutes after digoxin. Ps, 26; Pd₂, -2. Cardiac output 3.8 l./min.

FIG. 8.—Case No. 13. Development of left ventricular failure following digoxin. (A) Before digoxin. Right ventricular pressures: Ps, 31; Pd₂, -1. Arterial pressure 154/108. Cardiac output 3.2 l./min. (B) 27 minutes after 1.0 mg. digoxin. Ps, 65; Pd₂, 7. Arterial pressure 190/?. Cardiac output 2.1 l./min.

DISCUSSION

In ten of the fifteen patients the major measurable action of digoxin was to reduce an elevated pulmonary systolic pressure towards normal. We agree with Bloomfield *et al.* (1946), Hickam and Cargill (1948), and Lagerlof and Werko (1949) that the raised pulmonary arterial pressure is largely the result of a high pulmonary venous pressure behind the failing left heart. When the left ventricle fails, its systolic ejection is reduced, and to its residual blood is added the continuing inflow from the normally functioning right ventricle. After a few beats equality of output is restored at the expense of a higher diastolic filling pressure on the left side. The fall in pulmonary vascular pressures produced by digoxin represents a restoration towards normal working conditions of the left ventricle. The simplest explanation of the fall in pressure is that digoxin improves the emptying of the left ventricle, diminishes the volume of residual blood and so lowers the diastolic filling pressure. A temporary inequality of output in favour of the left ventricle, lasting a few beats, is undetectable by our methods.

The right ventricle under these circumstances may behave physiologically. When pulmonary vascular pressure falls, the right heart has less work to do, and the diastolic intraventricular pressure would be expected to fall with a parallel reduction in systemic venous pressure. Like a normally functioning heart, output frequently remains unchanged, or even falls slightly after digitalis.

Such an explanation is in accordance with standard pharmacological interpretation, and accounts more satisfactorily for the fall in venous pressure in the absence of cardiac output change, which previously seemed to demand the postulation of a primary action of digitalis on venomotor tone. The "stimulating" action of cardiac glycosides may thus occur without a manifest increase in cardiac output during the period of observation. In some cases the stimulating action is shown by an early increase in output which may of course be accompanied by the same reduction in pulmonary vascular pressures that have been described above and by Harvey *et al.* (1949).

Digitalis, however, has a complex set of circulatory actions, and we have to take into account a pressor effect on the systemic arterioles, and the altered functional state of the myocardium which determines the type and degree of digitalis response. In two instances the pressor response seemed to determine the development of left ventricular failure with a fall in cardiac output, raised pulmonary vascular pressures and pulmonary congestion. Our previous experience has included similar instances and such attacks do not seem to be mere coincidence following full intravenous doses of digoxin. It is possible that digoxin may have a pressor action on the pulmonary vascular bed in some instances; further studies which are in progress in pulmonary heart failure and valvular disease may throw further light on this and other outstanding problems.

SUMMARY

Fifteen cases of left ventricular failure due to hypertensive or ischaemic heart disease have been studied. Ten cases showed a reduction in right ventricular pressures after digoxin, which was not always accompanied by a measurable increase in cardiac output during the period of observation. These changes are attributed to differential "stimulation" of the failing left ventricle, a fall in pulmonary vascular pressure, and consequent unloading of the right ventricle with resulting fall in venous filling pressure.

Digoxin produced a hypertensive response in 8 cases, 3 of which developed a rise in right ventricular pressure and other signs of acute left ventricular failure. Two patients had an intermediate type of response with a rise in cardiac output without a fall in right ventricular pressure during the period of observation.

Acknowledgments are gratefully given to the Rockefeller Foundation for assistance in purchase of equipment, and to the Medical Research Council for a grant defraying other expenses. We are grateful for technical help to Dr. W. P. Small, Miss Margot McAdam, Mr. A. H. Latham and Mr. E. E. Barrett. Professor R. H. Goetz suggested the method of respiratory recording.

REFERENCES

- Ahmed, S., Bayliss, R. I. S., Briscoe, W. A., and McMichael, J. (1950). *Clin. Sci.*, **9**, 1.
 Bloomfield, R. A., Lauson, H. D., Cournand, A., Breed, E. S., and Richards, D. W. (1946). *J. Clin. Invest.*, **25**, 639.
 — Rapaport, B., Milnor, J. P., Long, W. K., Mebane, J. G., and Ellis, L. B. (1948). *Ibid.*, **27**, 588.
 Dock, W., and Tainter, M. L. (1930). *Ibid.*, **8**, 467.
 Douglas, C. G., and Priestley, J. G. (1948). *Human Physiology*, Oxford.
 Harvey, R. M., Ferrer, M. I., Cathcart, R. T., Richards, D. W., and Cournand, A. (1949). *Amer. J. Med.*, **7**, 439.
 Hickam, J. B., and Cargill, W. H. (1948). *J. Clin. Invest.*, **27**, 10.
 Howarth, S., McMichael, J., and Sharpey-Schafer, E. P. (1946). *Clin. Sci.*, **6**, 41.
 Lagerlof, H., and Werko, L. (1949). *Acta Cardiol.*, **4**, 1.
 Lambert, E. H., and Jones, R. E. (1948). *Proc. Mayo Clin.*, **23**, 487.
 McMichael, J., and Sharpey-Schafer, E. P. (1944a). *Quart. J. Med.*, **13**, 123.
 —, —, (1944b). *Brit. Heart J.*, **6**, 33.
 Pugh, L. G. C., and Wyndham, C. L. (1950). *Clin. Sci.* (In the press).
 Ryland, D. A. (1933). *J. Clin. Invest.*, **12**, 847.
 Stead, E. A., Warren, J. V., and Brannon, E. S. (1948). *Arch. intern. Med.*, **81**, 282.
 Warren, J. V., Brannon, E. S., Weens, H. S., and Stead, E. A. (1948). *Amer. J. Med.*, **6**, 193.
 Wiggers, C. J. (1928). *The Pressure Pulses in the Cardiovascular System*. London.