

Folic acid malabsorption in cardiac failure

R. D. HYDE AND C. A. E. H. LOEHRY

From the Royal South Hants Hospital, Southampton

The association of malnutrition with chronic cardiac failure has been recognized for many years, and the occurrence of intestinal malabsorption was first recorded in 1938 when Bologna and Costadoni measured, by fat balance, the degree of steatorrhoea in 20 patients with congestive cardiac failure. Malabsorption of neutral fat has been repeatedly observed (Langen, 1953; Hakkila, Mäkelä, and Halonen, 1960; Jones, 1961; Berkowitz, Croll, and Likoff, 1963) but impaired absorption of other nutrients is less well documented.

In the present study the intestinal absorption of folic acid has been investigated in patients with various types of congestive cardiac failure and the results have been related to other evidence of malabsorption. These observations have been compared with similar tests in normal subjects, in patients with folate deficiency without malabsorption, and in patients with steatorrhoea.

CLINICAL MATERIAL

PATIENTS WITH CARDIAC FAILURE Twenty-four patients with cardiac failure and one with cyanotic congenital heart disease were studied (Table I). The duration of the current episode of congestive failure was assessed from the history and outpatient records. Severe failure was defined by the presence of extensive oedema, ascites, and a jugular venous pressure raised above the angle of the jaw with the patient resting at 45 degrees. The cause of the heart disease was ischaemic in 13 patients, cor pulmonale in five, chronic rheumatic disease in five, and acute nephritis in one patient. The patient without failure had severe anoxia and Eisenmenger's syndrome. All were treated with digitalis and diuretics during the initial admission and patients with cor pulmonale received ampicillin. Where possible, those with evidence of malabsorption were studied again when the cardiac failure had been treated.

PATIENTS WITH FOLATE DEFICIENCY BUT NO EVIDENCE OF MALABSORPTION Folic acid absorption was studied in 13 patients with low levels of serum folate. There was no evidence of intestinal malabsorption and the folate deficiency was due to other causes.

NORMAL SUBJECTS Nine members of the medical and technical staff who had normal levels of serum folate were studied.

PATIENTS WITH MALABSORPTION Seven patients had steatorrhoea which was due to idiopathic steatorrhoea in three cases and to Crohn's disease, scleroderma, jejunal stricture, or Hodgkin's disease in the other patients.

METHODS

FOLIC ACID ABSORPTION The method followed that described by Chanarin, Anderson, and Mollin (1958) except that the oral dose of folic acid was related to body weight, 40 µg per kg being given. Sodium folate, 15 mg, was given intramuscularly each evening for three days. (The normal subjects received 4 oral doses of 15 mg.) About 36 hours after the last dose, the baseline blood sample was taken from the subject fasted overnight. The calculated dose of folic acid, dissolved in water, was given orally and samples of clotted blood were taken after one, two, and four hours.

Serum folic acid was assayed with *Streptococcus faecalis* R. In subjects who showed folate malabsorption and who had recently had antibiotic treatment, the absence of an antibiotic inhibitor in the assay tube was demonstrated by showing high *L. casei* activity in the serum and by demonstrating that the serum did not inhibit the activity of a known control serum, when mixed in equal proportions.

OTHER METHODS Serum folate was assayed using *Lactobacillus casei*. The observed range in 107 normal subjects was 2.0-16.0 ng per ml (mean 5.3 ng per ml).

Serum vitamin B₁₂ was assayed using *Lactobacillus leichmannii*. The observed range in 107 normal subjects was 138-1,000 pg per ml (mean 350 pg per ml).

Arterial blood gas tensions, pO₂ and pCO₂, were measured by the Astrup method within the first three days of admission.

Jejunal biopsy was performed with a Crosby capsule and the specimens were examined under a dissecting microscope and by sections stained with haematoxylin and eosin.

Absorption of fat was estimated from three or five-day faecal collections and the daily fat excretion estimated by ether extraction of acid hydrolysed dried faeces (Cambridge's method, modified). It is recognized that because of severe illness and anorexia some patients had a low dietary intake of fat.

Serum urea, serum albumin, or total protein and blood haemoglobin concentration were estimated by standard methods.

TABLE I

Case No.	Sex and Age (yr)	Heart Disease	Cardiac Failure		Blood (mm Hg)		Haemo-globin (g/100 ml)	Serum Urea (mg/100 ml)	Serum Folate (ng/ml)	Serum Folic Acid (ng/ml)				Faecal Fat (g/day)	Jejunal Biopsy
			Duration	Severity	pO ₂	pCO ₂				0 hr	1 hr	2 hr	4 hr		
1	M 66	Acute nephritis	2 wk		90	45	14.6	74	9.0	2	72	61	33	7.1	—
2	F 68	Isch.	2 wk		70	36	15.0	52	4.0	36	—	200	—	5.2	—
3	M 49	Rheum.	1 mth		75	41	13.4	45	7.3	2	136	107	64	—	Normal
4	M 76	Isch.	1 mth		70	41	15.6	164	2.1	20	146	156	132	5.1	Stomach
5	F 74	Isch.	1 mth		75	42	14.8	67	—	18	—	110	—	—	—
6	M 68	Isch.	1 mth		—	—	8.1	190	5.9	4	67	94	52	5.2	—
7	F 77	Isch.	1 mth		70	42	10.3	55	2.8	1	—	65	—	3.5	—
8	F 47	Rheum.	1 mth	Severe	80	—	14.4	64	4.6	2	80	73	36	0.5	—
9	F 69	Rheum.	2 mth		70	41	13.4	43	3.9	20	130	120	102	2.8	—
10	M 60	Isch.	2 mth		75	40	12.8	93	5.9	7	130	106	80	1.4	Normal
11	F 70	Isch.	2 mth		85	42	13.0	40	2.4	2	24	56	64	6.7	Normal
12	M 66	Rheum.	2 mth		80	45	12.4	52	—	1	45	51	41	—	Normal
13	M 66	Isch.	3 mth		69	40	11.7	61	—	1	51	54	43	—	Normal
14	M 69	Isch.	3 mth		66	44	12.7	109	2.9	2	35	48	39	5.6	Normal
15	M 39	Eisenmenger	None		59	40	18.8	16	20.0	2	92	105	56	2.7	Normal
16	M 60	Cor pulm.	1 mth	Severe	51	81	21.0	92	8.2	2	93	106	70	3.4	Villi + leaves
17	M 47	Cor pulm.	6 wk	Severe	23	66	16.4	72	3.2	1	66	64	28	2.8	Villi + leaves
18	F 65	Cor pulm.	1 mth	Severe	59	56	16.8	54	5.4	8	166	160	92	1.8	—
19	M 68	Cor pulm.	2 mth	Severe	52	61	14.6	52	5.7	15	—	200	160	—	—
20	M 70	Cor pulm.	3 mth	Severe	53	95	17.5	64	3.5	1	35	20	9	1.4	Villi + leaves
21	M 73	Isch.	2 mth	Severe	53	95	17.5	64	3.5	4	100	100	62	—	Villi + leaves
22	M 54	Isch.	2 mth	Severe	53	95	17.5	64	3.5	6	29	14	14	6.8	Villi + leaves
23	F 82	Isch.	3 mth	Died	86	33	13.0	39	9.6	1	1	1	1	0.8	Normal
24	F 71	Isch.	6 mth	Present	86	33	13.0	39	9.6	2	41	36	25	—	—
25	F 50	Rheum.	Years	Absent ¹	64	30	13.7	71	2.8	2	25	31	17	4.3	Normal
				Absent ¹	90	45	9.7	44	5.3	1	84	86	63	—	—
				Present	90	45	9.7	44	5.3	1	20	22	18	12.8	—
				Absent ¹	4	—	—	—	—	4	92	92	75	—	—
				Present	70	38	11.8	51	5.8	1	8	4	2	1.1	Villi + leaves
				Absent ¹	—	—	8.9	62	4.6	12	35	29	20	—	—
				Present	—	—	8.9	62	4.6	2	10	14	6	5.2	—
				Remained in failure											

Isch. = Ischaemic heart disease; Rheum. = rheumatic heart disease; Cor pulm. = Cor pulmonale.
¹Condition when absorption tests were repeated.

RESULTS

The results are summarized in Table I and Figure 1.

FOLIC ACID ABSORPTION In nine normal subjects the mean peak serum folic acid was 118 ng per ml (range: 95-146) and in 13 patients with folate deficiency but no malabsorption the mean was 99 ng per ml (range: 72-160).

Seven patients with steatorrhoea had peak serum folic acid concentrations of less than 22 ng per ml.

The five patients with cor pulmonale and one with Eisenmenger's syndrome all had arterial oxygen tensions of less than 60 mm Hg. Amongst these, two had folic acid malabsorption which was defined by a failure of the peak serum concentration to exceed 44 ng per ml. Folic acid absorption had returned to normal when one (case 19) was restudied 10 weeks later when no longer in cardiac failure. The other patient died during the first period of study. Four

of the 13 patients with ischaemic heart disease had folic acid malabsorption (cases 21-24) and all showed improved folic acid absorption when out of failure, two being entirely normal. One of the five patients with rheumatic heart disease had folate malabsorption (case 25). As there was no improvement in the clinical condition due to severe tricuspid incompetence, the absorption test was not repeated. The one patient with acute nephritis had normal folic acid absorption (case 1).

FAECAL FAT Studies in 21 patients showed normal fat excretion in all except two. One of these had folic acid malabsorption and the other was the patient with acute nephritis.

JEJUNAL HISTOLOGY Jejunal biopsy was successful in 14 patients and these included five of the seven patients with folic acid malabsorption. All were normal.

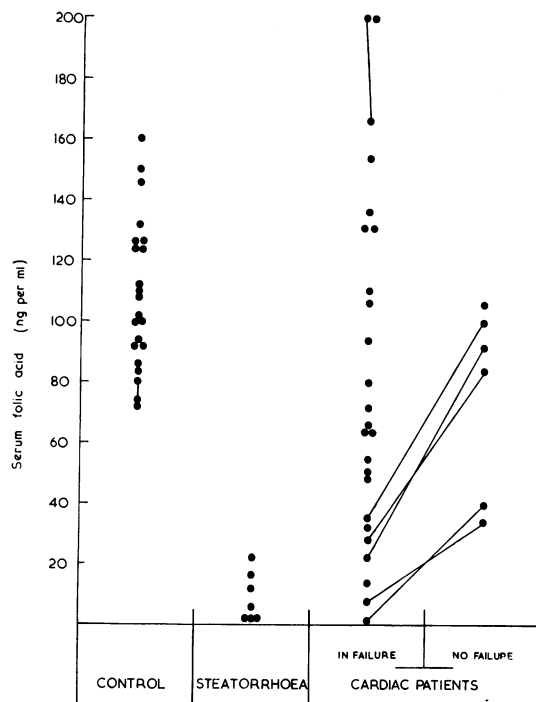


FIG. 1. Peak serum folic acid concentration with folic acid absorption test.

(●—● = separate investigations in the same subject)

OTHER FINDINGS The serum urea concentration was greater than 40 mg per 100 ml in all but one of the patients with cardiac failure, but it exceeded 100 mg per 100 ml in only three patients. Anaemia was present in three iron-deficient patients (cases 7, 23, and 25) and one with chronic pyelonephritis (case 6). Serum folate and serum vitamin B₁₂ were normal in all subjects studied. There was no excess of nuclear hypersegmentation in neutrophil polymorphs and no anaemia due to folate deficiency in the patients with folic acid malabsorption.

DISCUSSION

MALABSORPTION IN CARDIAC FAILURE Several investigators have described malabsorption of neutral fat in patients with congestive cardiac failure, although few have reported the high incidence recorded by Bologna and Costadoni (1938) who found that 12 out of 20 patients excreted at least 7 g of fat daily, when the daily intake was between 60 and 80 g. Pittman and Cohen (1965) described normal faecal fat and nitrogen excretion in 10 patients studied and Jones (1961) found steatorrhea in only three of 17 cases. In two additional patients

Jones described malabsorption of ¹³¹I triolein and other authors have found a higher incidence of abnormality in radioactive fat absorption (Hakkila *et al*, 1960). However, further experience has thrown considerable doubt on the validity of this method (Schwabe, 1965). In the present series, only two patients had steatorrhea although some may well have had a reduced dietary intake at the time of the test. There is little evidence of malabsorption of substances other than neutral fat. Absorption of oleic acid (Mäkelä, Hakkila, and Hakkila, 1960) and vitamin A (Pittman and Cohen, 1965) have been shown to be normal. Hardy and Schultz (1952) have reported impaired jejunal absorption of amino acids in two hypoproteinaemic cardiac patients.

FOLIC ACID ABSORPTION IN CARDIAC FAILURE The method of estimating folic acid absorption used in this study was introduced by Chanarin *et al* (1958) and has been shown to be a sensitive index of folate malabsorption. It is more sensitive than the measurement of urinary excretion after an oral dose of tritiated folic acid (Anderson, Belcher, Chanarin, and Mollin, 1960) and has the advantage of using serum concentrations so that it can be applied in renal failure. Most of the patients in the present study had renal impairment, although it was rarely severe. In these cases, any failure adequately to excrete the absorbed folic acid would tend to give a falsely high serum level and might make the low serum levels even more significant. The high fasting serum folic acid level at the beginning of the absorption test in eight of the patients may have been due to inadequate renal excretion of the intramuscular dose, or possibly the result of delayed absorption from the site of injection. Correction of the peak serum level for the high baseline activity did not alter the grouping of patients with regard to folic acid malabsorption.

Two other factors that might influence the results are the effect of antibiotics and delayed gastric emptying. Although ampicillin in doses of 1 g daily may inhibit growth in a *Lactobacillus casei* assay, such a dose had no effect on a *Streptococcus faecalis* assay of folic acid absorption in normal subjects. The antibiotic treatment of the three patients with cor pulmonale who had normal absorption did not differ from the two who showed malabsorption and none of the baseline sera showed evidence of inhibition in the assay. There was no evidence of delayed gastric emptying since in all except one patient the peak serum concentration occurred before the fourth hour of observation.

In this series, malabsorption of folic acid was observed in seven of 24 patients with cardiac failure and it improved significantly when the failure was

successfully treated. One patient (case 22) who was studied initially before cardiac failure developed, and four others who were reinvestigated when failure improved, all showed improved absorption when not in failure, and in three of these folic acid absorption came within the normal range. No significant change in the folic acid absorption was seen when one patient with severe cardiac failure was reinvestigated while still in failure (case 18). Comparison between those with and those without folic acid malabsorption showed no consistent difference in type of cardiac disease, degree of arterial hypoxia, or severity of failure. There was, however, a correlation with the duration of cardiac failure. None of the 10 patients with heart failure of less than two months' duration showed malabsorption whereas in the group of 13 patients with a longer history of cardiac failure, seven had malabsorption and a further three (cases 12 to 14) had peak serum folic acid concentrations which were only just within the normal range. Opinions among other investigators are divided; some found no relation with duration (Jones, 1961), while others suggest that severity is associated with malabsorption (Bologna and Costadoni, 1938). In the present study, chronicity appeared to be a more important factor.

The mechanism of malabsorption in cardiac failure is not understood. Impairment of pancreatic secretion has been reported (Masoni and Pellegrini, 1953) and finds some histological support in a post-mortem study of the pancreas in congestive cardiac failure (Nicol, 1961). While this might affect fat absorption, the absorption of folic acid is not dependent on pancreatic secretion and only one of seven patients with folic acid malabsorption had evidence of steatorrhoea. Anoxia has been suggested as a possible factor in malabsorption and several observers have reported steatorrhoea in severe anoxia. Pugh (1962) observed that when the alveolar oxygen tension was reduced to 45 mm Hg during the British Himalayan Expedition of 1960-61, the members complained of bulky and greasy stools, and impaired fat absorption has been demonstrated in rats at corresponding partial pressures of oxygen (Maclachland and Thacker, 1945). Previous studies in cardiac failure have not reported arterial blood gas tensions and very few subjects with cor pulmonale have been investigated. The present series included six patients with arterial oxygen tensions of less than 60 mm Hg, and there was no correlation between hypoxia and folic acid malabsorption. It has been suggested that local anoxia, due to portal venous congestion, may be an important factor (Langen, 1953). There have been several case reports of atherosclerotic mesenteric vascular occlusion producing malabsorption of fat, carbohydrate, and

vitamin B₁₂ (Shaw and Maynard, 1958; Joske, Shamma'a and Drummey, 1958) and small intestinal ischaemia has been described in patients with marked cardiac failure who have no mesenteric vascular lesion (Ende, 1958). There is no evidence of generalized villous atrophy in mesenteric vascular insufficiency but it is possible that prolonged venous congestion may produce a functional defect in the small intestinal mucosa without detectable structural abnormality.

Whatever the mechanism, the effects are readily reversible. Several investigators have recorded that steatorrhoea was diminished when cardiac failure improved (Bologna and Costadoni, 1938; Hakkila *et al*, 1960; Berkowitz *et al*, 1963) and in the present series it is probably this reversible and transient defect that accounts for the lack of evidence of folate deficiency in the patients studied. Folic acid is probably absorbed by an active transport mechanism (Burgen and Goldberg, 1962) although other authors, using *in vitro* methods, have postulated passive diffusion (Turner and Hughes, 1962) or alternative mechanisms depending upon the concentration (Luhby and Cooperman, 1964). If an active process is required for the absorption of physiological amounts of folic acid, it is possible that prolonged cardiac failure may influence it by an effect on the sodium pump of the epithelial cell. It is unlikely that digitalis had any direct effect in the present study since it was given to all patients. Overall, the present investigation, which demonstrated folic acid malabsorption in the presence of a normal epithelial surface area, favours an active transport mechanism.

SUMMARY

Twenty-five patients with cardiac disease have been investigated for evidence of malabsorption. Seven were found to have folic acid malabsorption but only one had steatorrhoea. Folic acid absorption was reassessed in five patients when out of cardiac failure and in all the absorption had significantly improved. There was no correlation between folic acid malabsorption and the jejunal biopsy appearance, arterial hypoxia, severity of failure, or type of cardiac disease. There was, however, correlation with the duration of cardiac failure.

REFERENCES

- Anderson, B., Belcher, E. H., Chanarin, I., and Mollin, D. L. (1960). The urinary and faecal excretion of radioactivity after oral doses of ³H-folic acid. *Brit. J. Haemat.*, **6**, 439-455.
- Berkowitz, D., Croll, M. N. and Likoff, W. (1963). Malabsorption as a complication of congestive heart failure. *Amer. J. Cardiol.*, **11**, 43-47.
- Bologna, A., and Costadoni, A. (1938). Osservazioni sulla funzione gastro pancreatici nei cardiopazienti. *Arch. ital. Mal. Appar. dig.*, **7**, 215-254.

- Burgen, A. S. V., and Goldberg, N. J. (1962). Absorption of folic acid from the small intestine of the rat. *Brit. J. Pharmacol.*, **19**, 313-320.
- Chanarin, I., Anderson, B. B., and Mollin, D. L. (1958). The absorption of folic acid. *Brit. J. Haemat.*, **4**, 156-166.
- Ende, N. (1958). Infarction of the bowel in cardiac failure. *New Engl. J. Med.*, **258**, 879-881.
- Hakkila, J., Mäkelä, T. E., and Halonen, P. I. (1960). Absorption of 131 I triolein in congestive heart failure. *Amer. J. Cardiol.*, **5**, 295-299.
- Hardy, J. D., and Schultz, J. (1952). Jejunal absorption of an amino acid mixture in normal and in hypoproteinemic subjects. *J. appl. Physiol.*, **4**, 789-792.
- Jones, R. V. (1961). Fat-malabsorption in congestive cardiac failure. *Brit. med. J.*, **1**, 1276-1278.
- Joske, R. A., Shamma'a, M. H., and Drummey, G. D. (1958). Intestinal malabsorption following temporary occlusion of the superior mesenteric artery. *Amer. J. Med.*, **25**, 449-455.
- Langen, C. D. de (1953). Steatorrhoea and the intestinal circulation. *Acta med. scand.*, **146**, 7-19.
- Luhby, A. L., and Cooperman, J. M. (1964). Folic acid deficiency in man and its interrelationship with vitamin B₁₂ metabolism. *Advanc. in Metab. Dis.*, **1**, 263-334 (see p. 268).
- Maclachlan, P. L., and Thacker, C. W. (1945). The effect of anoxia on fat absorption in rats. *Amer. J. Physiol.*, **143**, 391-395.
- Mäkelä, T. E., Hakkila, R. L., and Hakkila, J. (1960). Absorption of 131 I-oleic acid in congestive heart failure. *Acta med. scand.*, **167**, 121-136.
- Masoni, A., and Pellegrini, P. (1953). La funzionalità esocrina pancreatica nella stasi cardiaca. *Cuore e Circol.*, **37**, 171-179.
- Nicol, A. (1961). Fat-malabsorption in congestive heart failure. *Brit. med. J.*, **1**, 1537-1538.
- Pittman, J. G., and Cohen, P. (1965). Studies in intestinal absorption in chronic congestive heart failure. *Amer. J. Gastroent.*, **43**, 101-120.
- Pugh, L. G. C. E. (1962). Physiological and medical aspects of the Himalayan scientific and mountaineering expedition, 1960-61. *Brit. med. J.*, **2**, 621-627.
- Schwabe, A. D. (1965). *Nuclear Medicine*, edited by W. H. Bland, p. 273. McGraw Hill, New York.
- Shaw, R. S., and Maynard, E. P., III (1958). Acute and chronic thrombosis of the mesenteric arteries associated with malabsorption. *New Engl. J. Med.*, **258**, 874-878.
- Turner, J. B., and Hughes, D. E. (1962). The absorption of some B-group vitamins by surviving rat intestine preparations. *Quart. J. exp. Physiol.*, **47**, 107-123.