Clinical outcome of transfemoral embolisation in patients with arteriovenous malformations of the liver in hereditary haemorrhagic telangiectasia (Weber-Rendu-Osler disease)

M Caselitz, S Wagner, A Chavan, M Gebel, J S Bleck, A Wu, H J Schlitt, M Galanski, M P Manns

Abstract

***Background*—Arteriovenous malformations of the liver in Osler's disease may present as high output cardiac failure. A few case reports suggested that treatment with arterial embolisation may have beneficial effects in such patients.**

***Aims*—To investigate the efficacy and safety of this treatment modality in a prospective pilot study.**

***Patients and methods*—Four women and one man (aged 39–59 years) with the dominant hepatic manifestation of Osler's disease presented with symptoms of cardiac failure and elevated cardiac output. Arteriovenous malformations were treated in three to five sessions with arterial embolisation using coils. The outcome was analysed by measurement of cardiac output and scoring of clinical symptoms.**

***Results*—Embolisation was technically feasible in all patients and adequate occlusion of vascular malformations was achieved in four patients. After completion of therapy symptoms improved in four patients, while one patient suffered from abdominal pain due to cholangitis. One patient died seven months after the embolisation treatment from variceal bleeding. Mean cardiac output significantly decreased from 14.2 (range 12–17.3) l/min to 8 (range 5.9–10.6) l/min (p=0.043). After a median follow up of 23 months (range 7–50 months), three of five patients had a long lasting improvement of clinical symptoms and cardiac function.**

***Conclusions*—This first treatment series of patients with dominant hepatic involvement in Osler's disease indicates that arterial embolisation may prevent cardiac failure by significantly lowering cardiac output.**

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Keywords: hereditary haemorrhagic telangiectasia; Weber-Rendu-Osler disease; hepatic vascular malformation; cardiac failure; embolisation therapy

Department of Gastroenterology and Hepatology
M Caselitz
S Wagner
M Gebel
J S Bleck
M P Manns

Department of Radiology
A Chavan
M Galanski

Department of Abdominal Surgery, Medizinische Hochschule, Hannover, Germany
A Wu
H J Schlitt

Correspondence to:
Professor Dr M P Manns, Department of Gastroenterology and Hepatology, Medical School, Carl Neuberg Strasse 1, 30623 Hannover, Germany.

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Hereditary haemorrhagic telangiectasia (HHT) is also known as Rendu-Osler-Weber disease. It is an autosomal dominantly transmitted malformation of vascular structure with diverse manifestations. The classic clinical features are mucocutaneous telangiectasia, epistaxis, and a family history of HHT.[1]

The larger vascular malformations are described as arteriovenous shunts, which can be found in any organ, but most often in the lungs, central nervous system, and digestive tract, especially the liver.[1] Hepatic involvement is described in 8–31% of patients suffering from HHT.[2 3] The major pathological features are a so called "pseudocirrhosis" with abnormally dilatated vessels surrounded by a varying amount of stroma and arteriovenous malformations (AVM).[4 5]

Clinical symptoms are hepatomegaly and a bruit over the liver. Serum levels of γ-glutamyl transferase and alkaline phosphatase can be elevated. Clinical complications of the liver involvement depend on the anatomy of these shunts: malformations between the hepatic artery and the liver veins may lead to high output cardiac failure[5] and malformations between the hepatic artery and the portal vein may cause portal hypertension.[6]

The treatment of arteriovenous malformations of the liver is usually conservative. This treatment may fail, however, in patients with large AVM. There is some experience with surgical ligation of the feeding vessels[6 7] and liver transplantation.[2] On the other hand, there are a few encouraging case reports of embolisation of the feeding vessels.[6 8–10] In this pilot study we have prospectively investigated the clinical outcome of percutaneous embolisation in five patients with large arteriovenous malformations of the liver and symptoms of cardiac failure in HHT.

Patients and methods

PATIENTS

From 1991 to 1995 five consecutive patients with HHT and dominant hepatic arteriovenous malformations were included in this pilot study. All patients suffered from symptoms of cardiac failure and circulatory disturbance or complications of portal hypertension. HHT was diagnosed when at least two elements of the classic triad (mucocutaneous telangiectasia, epistaxis, and a family history of HHT) were present. The patients were screened for hepatic involvement by colour Doppler sonography and the hepatic vascular lesions were confirmed by angiography.

Table 1 summarises clinical details of the patients at referral. The group consisted of four women and one man with a mean age of 50 years (range 39–59 years). Mucocutaneous telangiectasia was present in all patients. Epistaxis was present in three patients and a positive

Table 1 Clinical details of patients at referral

	Patient 1	*Patient 2*	*Patient 3*	*Patient 4*	*Patient 5*
Sex	Female	Female	Female	Male	Female
Age	54	50	40	58	47
family history	+	+	+	+	−
Telangiectasia	Face	Face	Face	Face	Face
Epistaxis	−	−	+	+	+
Clinical symptoms of complications	Dyspnoea	Upper GI bleeding	Abdominal angina	Dyspnoea	Vitality decrease
	Nycturia	Left ventricular hypertrophy	Weight loss	Nycturia	Dyspnoea
	Left ventricular hypertrophy	Mitral insufficiency	Tricuspidal insufficiency	Vitality decrease	
	Arrhythmia	Ascites	Ventricular extrasystoles		
	Hypertension		Congested jugular veins		
	Ascites		Steal syndrome		
Hepatomegaly	+	+	+	+	+
Bruit over the liver	+	+	+	+	+
Alkaline phosphatase raised	+	+	+	+	+
GGT raised	+	+	+	+	+
Cardiac output (l/min) before therapy	15	17,3	13	12	12.5
Shunt	Arteriovenous	Arterioportal	Arteriovenous	Arteriovenous	Arteriovenous
Number of embolisations	3	3	5	3	3

GGT, γ-glutamyl transferase; GI, gastrointestinal.

family history was also found in three patients. There were clinical symptoms of chronic high output cardiac failure due to arteriovenous malformations in four patients. One patient suffered from arterioportal shunts, which led to complications of portal hypertension (ascites, gastrointestinal bleeding). Extrahepatic visceral involvement was detected in two patients. One patient had arteriovenous malformations around the right kidney and in the retroperitoneum. In another patient arteriovenous shunts and collateral vessels were detected in the mesentery. These mesenteric malformations led to symptoms of abdominal angina due to a steal syndrome.

All patients had anicteric cholestasis with elevation of γ-glutamyl transferase activity. Four patients had increased alkaline phosphatase activity. Cholinesterase levels and prothrombin time were normal in all patients. No signs of cirrhosis were found in any patient. All patients underwent right heart catheterisation and echocardiography before and after embolisation and at the end of follow up to measure cardiac output.

To assess the clinical benefit of arterial embolisation a clinical score was developed (table 2). The general symptoms (decrease in vitality, weight loss), abdominal symptoms (pain, ascites) and cardiac symptoms (nycturia, dyspnoea) were each graded. The decrease in vitality was classified according to a severity index (0 = no restrictions; 1 = feeling of weariness; 2 = inability to work; 3 = hospitalisation). Weight loss and nycturia were also graded into four groups. The severity of pain was estimated and graded depending on the drugs required. Dyspnoea was classified according to the grading of the American Heart Association. Varicosis of the oesophagus was graded according to the classification of Paquet.[11] The total clinical score (0–9) was calculated by obtaining the sum of the means of the symptom categories (general symptoms, abdominal symptoms, cardiac symptoms).

EMBOLISATION TECHNIQUE

All patients underwent three to five sessions of transfemoral arterial embolisation of hepatic vascular malformations. The procedures were performed over a period of 4–20 weeks. The intervention was carried out under local anaesthesia and intra-arterial analgesics were given when required.

Using a transfemoral approach an abdominal aortography was initially performed followed by indirect mesentericoportography over the superior mesenteric artery or splenic artery. The hepatic artery branches were selectively catheterised and the AVM were embolised

Table 2 Criteria for clinical score

	Score			
	0	*1*	*2*	*3*
General symptoms				
Decrease in vitality	No restrictions	Increased fatigue	Treated as outpatient	Treated in hospital
Loss of weight in patients without ascites	None	<2 kg	<5 kg	>5 kg
Abdominal symptoms and findings				
Abdominal pain	None	No analgesics necessary	Analgesics necessary	Morphine like analgesics necessary
Ascites	None	Few	Moderate	Severe
Oesophageal varices	None	Grade 1–2	Grade 3	Grade 4
Cardiac symptoms				
Nycturia	None	1–2	2–3	>3
Dyspnoea	None	On strong exertion	On light exertion	At rest

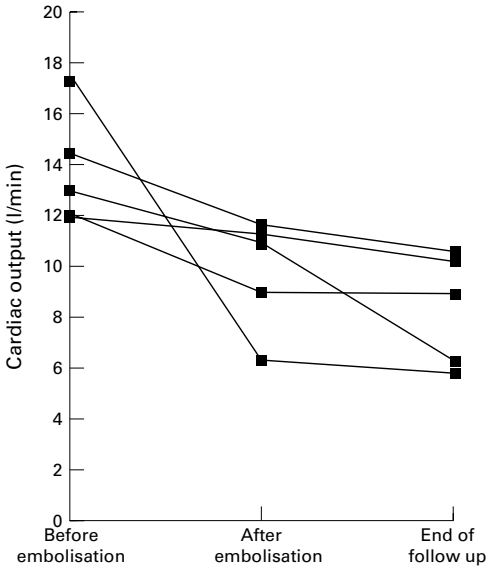

Figure 1 Comparison of cardiac output before and after embolisation and at the end of follow up.

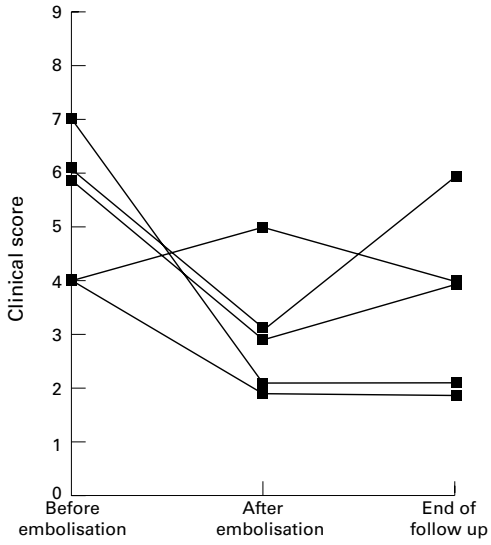

Figure 2 Comparison of the clinical score before and after embolisation and at the end of follow up.

peripherally with polyvinylalcohol particle coils (Ivalon, size 250–1180 μm; Interventional Therapeutics Corporation; South San Francisco, CA, USA) followed by proximal embolisation of large feeding arteries using platinum or steel coils (2–8 mm in diameter; MReye William Cook Europe A/S, Bjaeverskov, Denmark). The extent of the embolisation and the material used varied according to the clinical findings, the vascular anatomy of the patient, and the results of previous treatments. The result of the embolisation was documented by angiography.

FOLLOW UP

Patients were followed for a median of 23 months (range 7–50 months) after the last embolisation. Cardiac output was measured by right heart catheterisation and echocardiography after completion of treatment and at the end of follow up. Response to treatment was statistically analysed by comparing clinical scores and cardiac output before treatment, after completion of treatment, and at the end of follow up using the Wilcoxon signed rank test to test for matched pairs.

Results

Selective embolisation of the hepatic vascular malformations was technically feasible in all patients and complete occlusion of the malformations was achieved in four patients. In one patient embolisation was incomplete.

After completion of treatment mean cardiac output significantly decreased from 14.2 (range 12–17.3) l/min to 9.8 (range 5.9–10.6) l/min. This significant decrease was maintained after median follow up of 23 months (8 l/min; $p<0.05$) (fig 1).

After treatment, the clinical score decreased from 5.6 (7–4) to 3 (2–5) ($p=0.078$, NS) (fig 2) and remained virtually unchanged until the end of follow up (median 23 months). The treatment was well tolerated in four patients. Minor side effects were noted immediately after embolisation includingmoderate pain and nausea, which persisted for up to one to three days. They were controlled easily by analgesics and antiemetics. Laboratory tests showed a transient increase in leucocytes, alkaline phosphatase, and γ-glutamyl transferase. Serum concentrations of albumin and cholinesterase remained unchanged after embolisation.

There was an impressive improvement in clinical symptoms in the patient suffering from abdominal angina. After embolisation, body weight increased and analgesic treatment was discontinued.

One patient suffered from ischaemic cholecystitis and relapsing cholangitis with severe abdominal pain necessitating discontinuation of treatment. In this patient a reduction in cardiac output was not achieved immediately at the end of the embolisation, but during the follow up after 28 months.

Table 3 Review of the literature:transfemoral arterial hepatic embolisation in patients with HHT

Authors	*Number of patients*	*Age (y)*	*Sex*	*Shunt type*	*Number of embolisations*	*Follow up*
Zentler Munro *et al*[6]	1	51	M	Arterioportal	1 (additional ligation of the hepatic artery)	6 months
Derauf *et al*[8]	1	48	F	Arteriovenous	2	2 months, stable
Göthlin *et al*[9]	2	53	F	Arteriovenous	2	Died after 2 months
		41	F	Arteriovenous	1	24 months, stable
Nikolopoulos *et al*[10]	1	45	F	Arteriovenous	1	84 months, stable
Allison *et al*[12]	1	–	–	Arteriovenous	1	None
Bourgeois *et al*[13]	1	66	F	Arteriovenous	2	Died after 3 weeks
Brohee *et al*[14]	1	45	F	Arteriovenous	2	24 months, stable
Roman *et al*[15]	1	62	F	Arteriovenous	1	2 months, stable
Whiting *et al*[16]	1	71	F	Arteriovenous	3	None

One patient died seven months after the last embolisation. Her death was not related to the treatment. Although cardiac output had decreased from 17.3 l/min to 5.8 l/min, portal hypertension recurred after temporary improvement. The patient was readmitted six months after the third embolisation due to critical bleeding from oesophageal varices.

Discussion

This study shows that the clinical course of HHT patients with dominant hepatic involvement and symptoms of cardiac decompensation can be favourably influenced by arterial embolisation. Embolisation therapy was technically feasible, safe, and minimally invasive in our patients. Our study confirms preliminary results obtained from recent case reports (table 3).[6 8–10 12–16]

The clinical course of hepatic involvement in patients with HHT depends on the anatomy of the vascular malformations. Shunting between the hepatic artery and hepatic veins may lead to high output cardiac failure[5] and to a steal syndrome with symptoms of abdominal angina as shown in one of our patients. After embolisation the patient's symptoms improved remarkably, suggesting that a steal syndrome due to hepatic and mesenteric malformations can be treated efficiently by embolisation of branches of the hepatic artery.

Shunts between the hepatic artery and the portal vein occur rarely and may lead to portal hypertension.[6] One patient (patient 3) in our study suffered from portal hypertension. Although a decrease in cardiac output from 17.3 l/min to 5.9 l/min after embolisation was achieved, portal hypertension recurred soon after temporary improvement and led to critical bleeding from oesophageal varices. Similarly Zentler Munro *et al* described a patient with HHT suffering from portal hypertension due to arterioportal shunts in the liver.[6] The patient was treated with embolisation and ligation of the hepatic artery. These few reported cases in the literature may indicate that portal hypertension due to arterioportal shunts in patients with HHT cannot be controlled adequately by arterial embolisation alone. A portovenous shunt seems to be contraindicated in these patients because it would increase the flow in the arterioportal shunt and thereby probably elevate the central venous blood pressure significantly in patients with symptoms of cardiac failure. For these patients liver transplantation may be the most promising treatment modality, presuming that vascular malformations are restricted to the liver.

In general, embolisation treatment was well tolerated. The most frequent side effects observed in our patients were nausea and abdominal pain in the upper right quadrant. The pain persisted for a few hours to up to three days after embolisation and responded to non-opiate analgesics and antiemetics. Similar experiences have been reported in the literature.[8] A significant side effect was seen in one patient, who presented with ischaemic cholangitis and cholecystitis complicated by severe pain and nausea.

In the long run conservative treatment in patients with symptoms of cardiac failure due to dominant hepatic involvement may not be sufficient. Therefore, alternative therapeutic options must be considered. Various options for treatment are described including resection, ligation of the hepatic artery,[6 7] and liver transplantation.[2]

In our patients we saw a long lasting effect of interventional treatment up to 50 months after the last embolisation. Nikolopoulos *et al* reported a single case, who remained stable over a period of seven years.[10] Further investigations are required to confirm the stability of the long term results after arterial embolisation. Vascular malformations may potentially reappear and require further embolisations. In case of recurrent symptoms of heart failure in the long term a liver transplantation must be considered as alternative treatment. For primary management of these patients, however, arterial embolisation should probably be tried.

Since embolisation is far less invasive than liver transplantation, our study helps to establish embolisation as a treatment modality for these selected patients, which should be controlled in larger series.

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