

The outcome of angiography in patients with Raynaud's phenomenon: An unexpected role for atherosclerosis and hypercholesterolemia

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Abstract

Objective

Upper extremity angiography can make an important contribution to the diagnosis in vasculopathy. The present study was designed to assess the diagnostic role of upper extremity angiography in patients with disturbed circulation of the hand, according to a standardised protocol.

Methods

The study was carried out in an outpatient setting in 103 patients suffering from bilateral Raynaud's phenomenon without any obvious underlying disease and who were unresponsive to nifedipine and aspirin. All patients had angiographies taken according to a standardized technique using vasodilating medication, and reviewed according to a standardised protocol that covered all the known characteristics of angiopathy such as diminished flow, stops, tortuosity, irregularity of the wall, tapering, collaterals and blushing.

Results

Standardised angiograms showed vasculopathy compatible with primary vasospasm in 42 patients [all women; mean age 35.1 years], atherosclerotic vascular disease in 44 patients [M/F 9/35; mean age 46.7 years], peripheral embolism in 8 patients [M/F 4/4; mean age 38.4 years], vasculitis in 3 patients [3 women; mean age 38 years] and Buerger's disease in 3 patients [3 men; mean age 47 years]. Inter-observer differences were present in 4 cases, but consensus could be reached through open discussion. An unexpected 47% of patients with atherosclerotic vascular disease had dyslipidemia, frequently of familial origin.

Conclusions

The standardised angiography protocol proved to be helpful in the assessment of upper extremity angiography. Surprisingly, a high prevalence of angiographic abnormalities compatible with atherosclerotic vascular disease could already be diagnosed in relatively young patients with Raynaud's phenomenon, of whom 47% showed hypercholesterolemia.

Key words

Raynaud's phenomenon, hand angiography, classification angiopathy, hypercholesterolemia.

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Introduction

Hand ischemia or Raynaud's phenomenon may have multiple causes which range from trauma to the vasculitis as seen in systemic connective tissue diseases (1). In most of these disorders Raynaud's phenomenon is one of the most obvious and early manifestations, e.g. scleroderma and polymyositis (2). Suggestive evidence also exists in primary Raynaud's phenomenon that digital vasospasm is but one feature of a more generalized disorder. This notion is supported by one cross-sectional study of women with Raynaud's phenomenon in which a higher than expected prevalence of anterior chest pain was demonstrated (3). Most patients with Raynaud's phenomenon have normal arteries at rest and are only symptomatic after exposure to cold or emotional stress which induces palmar and digital artery vasospasm. Patients with permanent small artery obstruction often have persistent symptoms of hand ischemia, including pain at rest and ulceration, in addition to marked sensitivity to cold exposure. In view of the fact that Raynaud's phenomenon can be symptomatic of many different disorders requiring alternative approaches to therapy, a diagnostic work-up including upper extremity angiography is currently seen as the best practice (1). This holds notably for those patients with serious Raynaud's phenomenon non-responsive to therapy. However, the literature on the arteriographic examination of the upper extremities is fragmentary (4, 5) and no general consensus exists with regard to the technique used or the assessment of the angiography.

In order to evaluate the outcome of angiography in patients with symptoms of hand ischemia without any obvious underlying disease and unresponsive to medical therapy, and to determine the cardiovascular risk factors in these patients, we performed the following study, making use of a standardized scoring system.

Patients and methods

From 1984 to 1998, 103 patients who underwent angiography of the hand for bilateral Raynaud's phenomenon with-

out any obvious underlying disease, not responding to therapy (nifedipine, aspirine), were included in this study. Patients with diabetes mellitus, connective tissue disease and users of ergot alkaloids were excluded. All arteriograms were performed at the Department of Radiology of the Academical Medical Center Amsterdam. The study group consisted of 86 women and 17 men with a mean age at the time of angiography of 41.1 years (range of 20-62). Two patients had bilateral angiography and 7 patients had a second angiography at follow-up.

The medical records of these patients were reviewed carefully. The data collected included the patient's history with particular attention to trauma, tobacco use, oral contraceptives, medication, symmetry of symptoms and any family history of cardiovascular disease. The following laboratory data were included; glucose, cholesterol, triglycerides, rheumatoid factor, antinuclear antibodies, antibodies against extractable nuclear antigens (ENA), and anticardiolipin antibodies. Hypercholesterolemia was defined as a total cholesterol level > 6.2 mmol/liter and familial hypercholesterolemia was confirmed by DNA-diagnosis of the LDL-receptor gene mutation.

All upper extremity angiographies were carried out according to a standardized technique of direct puncture of the brachial artery with a 20-gauge needle, using 20 cc low osmolality or non-ionic contrast medium with an injection velocity of 3 cc/sec. In each session vasodilating medication, 1 ml (10 mg) tolazoline hydrochloride (Priscoline) diluted in 9 ml isotonic salt, was used and injected very slowly in the brachial artery. If no satisfactory vasodilatation was achieved a subsequent 1 ml tolazoline was injected.

Forty-nine angiographies of the right arm and 53 of the left arm were performed. In 19 of these cases angiography was performed using a transfemoral catheterization technique (Seldinger) because of vasospasm during percutaneous brachial artery puncture. In one patient with severe arterial spasm, a decision was made not to perform a Seldinger to prevent endovascu-

lar damage. One hundred and three angiograms were reviewed by an interventional radiologist (PD) and two readers in tandem [an internist (LK) and a rheumatologist (RV)]. All readers were blinded to the results as well as to the patient's history and laboratory results. The angiograms were reviewed according to a standardised protocol (Table I) that covered all of the known characteristics of angiopathy such as diminished flow, stops, tortuosity (corkscrew), irregularity of the wall, tapering, collaterals and blushing. The severity of vasculopathy was scored as 0 (none), 1 (slight) and 2 (evident).

Primary vasospasm (Fig. 1) was defined as tapering and a stretched course of the finger arteries with a normal aspect of the proximal arteries. Atherosclerotic vascular disease (Fig. 2) was defined as a tortuous course, with sometimes a corkscrew formation, and stops and collaterals of fragile arteries. Embolism was defined as an acute stop in an otherwise normal artery and the formation of collaterals

(Fig. 3) at a later stage. Vasculitis (Fig. 4) was defined as an irregularity of the vascular wall leading to obstruction and tapering of the proximal and distal arteries. Buerger's disease (Fig. 5) often has the same angiographic presentation as vasculitis but reveals the characteristic segmental pattern of involvement with a corrugated or "rippling" pattern of the arteries and multiple very tiny collateral vessels around the occluded segments (tree roots).

Results

Using the standardised protocol, angiograms showed vasculopathy compatible with primary vasospasm in 42 patients (all women; mean age 35.1 years, range 20-52), atherosclerotic vascular disease in 44 patients (9 men and 35 women; mean age 46.7 years, range 29-62), peripheral embolism in 8 patients (4 men and 4 women; mean age 38.4 years, range 23-54), vasculitis in 3 patients (3 women; mean age 38 years, range 28-55) and Buerger's disease in 3 patients (3 men; mean age 47 years, range 37-57) (Table II). Two

patients showed a normal aspect of the angiogram and in one patient angiography was not interpretable due to severe arterial spasm. Inter-observer difference was present in 4 cases and consensus was reached through open discussion.

In one patient with angiographic signs of vasculitis a muscle biopsy was performed and vasculitis was confirmed histologically (Fig. 6). In two patients in the embolism group the occlusion was due to costoclavicular compression and in one patient it was due to trauma (hypothenar hammer syndrome). In some cases of severe arterial obstruction a normal "blush" of the fingertips was observed, suggesting vascularisation from the venous side of the vasculature.

Twenty of the 42 patients (47%) with signs of atherosclerotic vascular disease exhibited dyslipidemia at laboratory examination. The prevalence of hypercholesterolemia was significantly higher in patients with atherosclerosis than in the other groups (20 versus 7 patients). Eight of the 20 patients

Table I. Standardised protocol used for scoring, covering all characteristics of vasculopathy.

Name:		Examination date:			L/R		
Birthdate:		Age:					
Artery:	Flow	Stops	Tortuosity	Irregularity Wall			
Radial							
Ulnar							
Arcus					Number	Collaterals	
Peripheral	Rad. Uln	Rad.Uln.	Rad. Uln.	Rad. Uln.	Blush	Collaterals	Tapering
Digit. 1							
Digit. 2							
Digit. 3							
Digit. 4							
Digit. 5							
Remarks :							0=None 1=Slight 2=Evident
Diagnosis :							



Fig. 1. Arteriogram of a patient with primary vasospasm characterised by tapering of the finger arteries with a normal aspect of the proximal arteries.



Fig. 3. Arteriogram of a patient with embolism characterised by an acute stop in an otherwise normal artery and the formation of collaterals.



Fig. 5. Arteriogram of a patient with thromboangiitis obliterans showing segmental occlusion of the radial, ulnar and digital arteries with tree root-like, multiple, very tiny collateral vessels around the occluded segments.

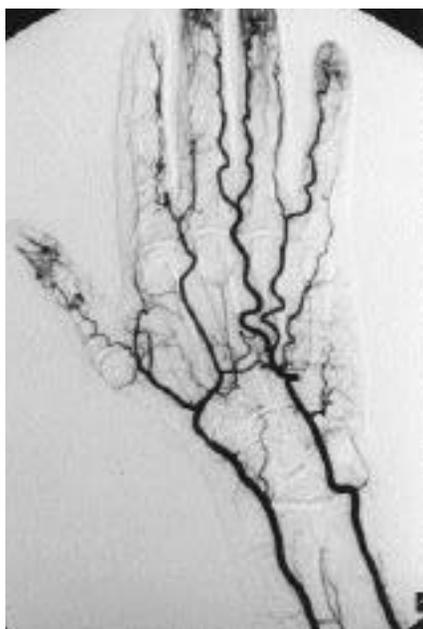


Fig. 2. Arteriogram of a patient with atherosclerosis characterised by a tortuous course, occasional corkscrew formation, and stops and collaterals of fragile arteries.



Fig. 4. Arteriogram of a patient with vasculitis characterized by irregularity of the vascular wall leading to obstruction and tapering of the proximal and distal arteries.

proved to have familial hypercholesterolemia (FH) as confirmed by the presence of a mutation in the LDL-receptor gene. The prevalence of smoking (23% vs 14%) and a positive family history of cardiovascular disease (28% vs 9%) was also significantly higher in the subjects with atherosclerotic vascular disease than in the primary vasospasm group. Contraceptives were used by 3 patients in the atherosclerosis group and by 9 patients in the primary vasospasm group (Table III).

The incidence of ANA positivity seemed somewhat higher in the group of patients with primary vasospasm but was no different from incidence in the general population (6). No significant difference was found between the different groups concerning the other aspects of the history or the laboratory data.

Discussion

Four weeks after the general discovery of X-rays on November 8th, 1895 by Wilhelm Konrad Roentgen, two resi-

Table II. Characteristics of patients in the different groups of vasculopathy.

	Primary vasospasm (n=42)	Atherosclerosis (n=44)	Embolism (n=8)	Vasculitis (n=3)	Buerger's disease (n=3)
Sex (m/f)	0/42	9/35	4/4	0/3	3/0
Age (y)	35.1 (20-52)	46.7 (29-62)	37.2 (23-54)	38 (28-55)	47 (37-57)
Asymmetrical	0	7	3	0	0
Smoking % (n)	14% (6)	23% (10)	62% (5)	NONE	100% (3)
ANA	3+	1+	0	2+	0

n = number of patients included; ANA: + = positive

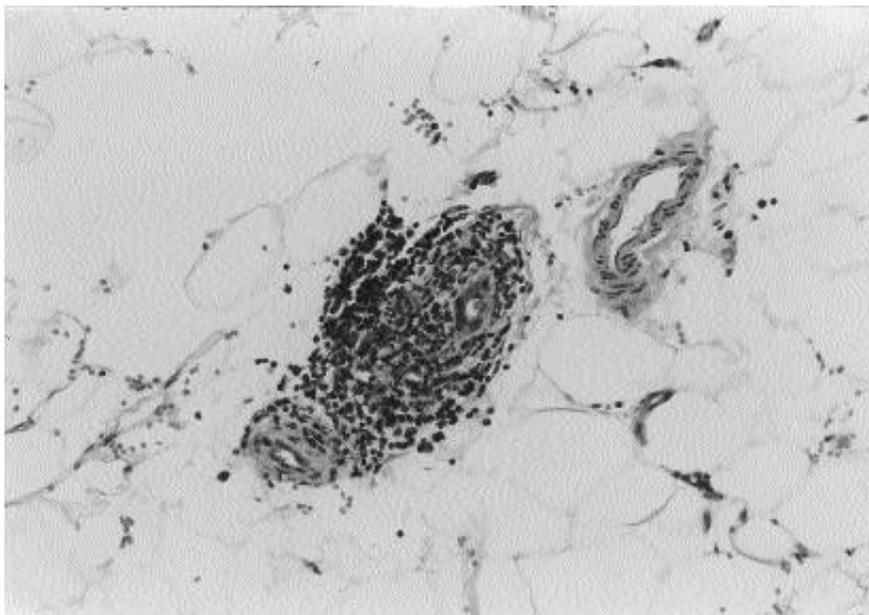


Fig. 6. Muscle biopsy specimen of patient with vasculitis showing lymphocytic small vessel vasculitis (courtesy of J. Lindeman, MD).

Table III. Characteristics of patients with primary vasospasm and atherosclerosis.

	Primary vasospasm (n=42)	Atherosclerosis (n=44)	Atherosclerosis (women: 35)	Atherosclerosis (men: 9)
Sex (m/f)	0/42	9/35	—	—
Age (y)	35.1 (20-52)	46.7 (29-62)	45.8 (30-62)	46.2 (29-62)
Smoking % (n)	14% (6)	23% (10)	17% (6)	44% (4)
Anticonception % (n)	22% (9)	9% (3)	9% (3)	—
Glucose mean (SD)	4.7 (0.77)	4.8 (0.68)	4.7 (0.66)	5.2 (0.66)
Cholesterol mean (SD)	5.3 (0.91)	6.3 (1.33)	6.2 (1.41)	6.6 (0.95)
Triglycerides mean (SD)	1.17 (0.72)	1.53 (0.74)	1.3 (0.59)	2.2 (0.75)
Hypercholesterolemia % (n)	15% (6)	47% (20)	42% (14)	66% (6)
Positive family history CVD % (n)	9% (4)	28% (12)	18% (6)	66% (6)

n = number of patients included SD = standard deviation

dents of the Second Institute of Physics and Chemistry in Vienna, E. von Haschek and O.T. Lindenthal, demonstrated upper extremity arteriography before a small audience, including W.K. Roentgen. The report on this first arteriogram of the upper extremity was published in an article entitled 'Ein Beitrag zur praktischen Verwertung der Photographie nach Roentgen' (7). As the applications of this diagnostic method seem to have almost fully crystallized, the number of publications has decreased in the last few years.

Different techniques are used worldwide (5) and no consensus exists with regard to the preferred method for assessing and carrying out angiography. In this study, the results of 103 upper extremity angiograms in a group of well-defined patients are described, performed by an interventional radiologist (PD) with a long experience in percutaneous brachial artery puncture. The advantages of this technique not only include the possibility of performing it in an outpatient setting but also the reduced risk of complications. One of the most frequent phenomena in peripheral angiography is vasospasm caused by local mechanical (puncture, guidewire) or chemical (contrast medium) irritation. Severe vasospasm does not permit optimal filling of the arterial lumen with contrast medium and makes a reliable diagnosis impossible. All of our angiograms were performed according to a standardized technique using a vasodilating agent (priscoline). In 20 patients local arterial vasospasm was induced by direct puncture of the brachial artery, making transfemoral catheterization necessary in 19 cases.

The patients included in this study had moderate to severe ischaemic complaints without a certain diagnosis. All had a "biphasic" phenomenon, or the classic "triphasic" bilateral Raynaud's phenomenon. Patients with known underlying disease (for example, inflammatory connective tissue diseases, e.g. scleroderma and polymyositis), which are sufficient causes for Raynaud's phenomenon themselves, were excluded. This explains the low incidence of vasculitis or vasculopathy

as seen in the context of connective tissue disorders and the unexpectedly high prevalence of atherosclerotic vascular disease underlying Raynaud's phenomenon, which was not seen previously (8). Hypercholesterolemia was also frequently found in this condition. A high prevalence of atherosclerotic vascular disease (44 patients) was established of which 20 patients (47%) showed some form of dyslipidemia. Further investigation revealed in 8 patients classical familial hypercholesterolemia as diagnosed by physical signs and symptoms and a mutation in the LDL-receptor gene. The prevalence of other vascular risk factors like smoking (23% vs 14%) and a positive family history (28% vs 9%) of premature cardiovascular disease was significantly higher in these subjects than in the primary vasospasm group, as was to be expected.

The diagnosis of vasculitis is usually based upon clinical and pathological findings, together with immunodiagnostic tests (9). Angiography may, however, provide important information in certain patients, both in terms of diagnosis and in the assessment of the extent of the disease.

Furthermore, a substantial amount of knowledge concerning the mechanisms that may link inflammation, immunity, and infections to the molecular and cellular events in the arterial wall leading to atherosclerotic lesions suggest that vasculitis may play a significant role in atherosclerosis (10, 11).

Performance of upper extremity angiography in all patients with bilateral Raynaud's phenomenon would result in a great number of normal studies, with consequent superfluous costs in health care and an increased risk of complications. On the other hand, lim-

iting the use of angiography bears the risk of missing the diagnosis in patients who would benefit from further evaluation of their vasculopathy or revascularisation (1) provided the angiographic technique is standardised as in this protocol. In either the direct puncture or the Seldinger technique no more than 3 ml/sec contrast should be used. An important role could be played by magnetic resonance angiography but this technique currently does not provide sufficient resolution for small vessel depiction. Other promising non-invasive techniques such as high-resolution ultrasonographic measurement of the artery intima and media thickness (IMT) are only applicable to the carotid artery, but do provide accurate and reliable measurement of atherosclerosis in the subclinical stages (12).

In our opinion, the advisability of conducting angiography in patients with hand ischemia will depend on the symmetry and severity of symptoms, the response to therapy, and the presence of various risk factors present in each patient. We found that only 47% of patients with signs of atherosclerosis showed dyslipidemia, which underscores the fact that current knowledge of risk factors cannot explain all cases.

In conclusion, percutaneous brachial angiography, performed by an experienced intervention radiologist using vasodilating medication, proved to be the preferred method for optimal visualization of the anatomical details of the arteries of the hand. Our standardised protocol appeared to be helpful in the assessment of angiography. Lastly, we demonstrated an unexpectedly high prevalence of atherosclerotic vascular disease and dyslipidemia in these patients with Raynaud's phenomenon.

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Dr. P.F. Dijkstra died shortly after the completion of this manuscript. We have lost a good friend and an excellent radiologist who made a great contribution to skeletal radiology.

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