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Abbreviations

PRP	Primary Raynaud's phenomenon
RP	Raynaud's phenomenon
SSc	Systemic sclerosis

Key Points

1. Primary Raynaud's phenomenon (PRP) is common especially in women.
2. PRP (unlike systemic sclerosis) does not progress to irreversible tissue injury: therefore if ulcers or digital pitting are present then this is *not* PRP and a secondary cause should be looked for.
3. Patients with PRP should have no features on history and examination of an underlying secondary cause. They should have a normal full blood count normal erythrocyte sedimentation rate, negative antinuclear antibody and normal nailfold capillaroscopy.
4. Most patients with PRP can be reassured and do not require drug treatment: in many patients symptoms improve spontaneously over the years.

5. If drug treatment is required a calcium channel blocker is the first choice.

Introduction

Primary (idiopathic) Raynaud's phenomenon (PRP) is important to both clinician and researcher for several reasons. First, it is very common (and is by far the most common cause of Raynaud's phenomenon [RP]). Second, although generally considered "benign" in that it does not progress to digital ulceration and critical ischaemia, PRP can be associated with significant pain and disability in those severely affected. Third, PRP must be distinguished from early systemic sclerosis (SSc), of which RP is often a presenting feature [1–3] and from RP secondary to other causes. Fourth, researchers often compare PRP to SSc-related RP in order to understand why patients with SSc (but not with PRP) progress to ischaemic injury.

A comprehensive review article on PRP should cover definition, epidemiology, genetic factors, pathogenesis, presenting features (history and examination), investigations and management, and also "transition" from primary to secondary RP. However, many of these different topics are covered in other chapters. The aim of this chapter is to give a short overview with cross-referencing to other chapters for further details. To put the problem into context, first a case of "typical" PRP is described.

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Case History

A 21-year-old student consults her general practitioner complaining of coldness and colour changes of her hands for approximately 3 years, worse when out of doors or in other cold environments. In the cold her fingers turn pale/blotchy (Fig. 6.1) then purple. Her feet tend to feel cold but less so than her hands. She is worried because her symptoms have become worse since she recently started working two evenings a week in a local supermarket: if she packs in



Fig. 6.1 Pallor phase in a patient with PRP

the freezer areas (which she does much of the time) her fingers become numb and painful as well as change colour. She is on no drug treatment and is a non-smoker. Her mother has similar symptoms and is in good general health: her maternal aunt has heart trouble as well as cold hands.

On examination there are no abnormalities. The skin of her fingers is cool but normal. Her upper limb peripheral pulses are easily felt.

Her general practitioner thinks that there is unlikely to be any significant cause of concern but arranges some further checks. Full blood count and erythrocyte sedimentation rate (ESR) are both normal and antinuclear antibody (ANA) testing negative. Nailfold capillaroscopy, performed at the local rheumatology department, is normal (Fig. 6.2).

A diagnosis of PRP is made. The patient is advised to speak to her employer and ask if she can change to working in warmer parts of the store: if this proves impossible then she is aware that it would be best to seek alternative part-time work. She is given a leaflet on RP, which gives information on keeping warm. Her doctor discusses starting nifedipine, but both he and the patient feel that this may not be necessary and the patient is concerned about the possibility of developing headaches, especially because this is

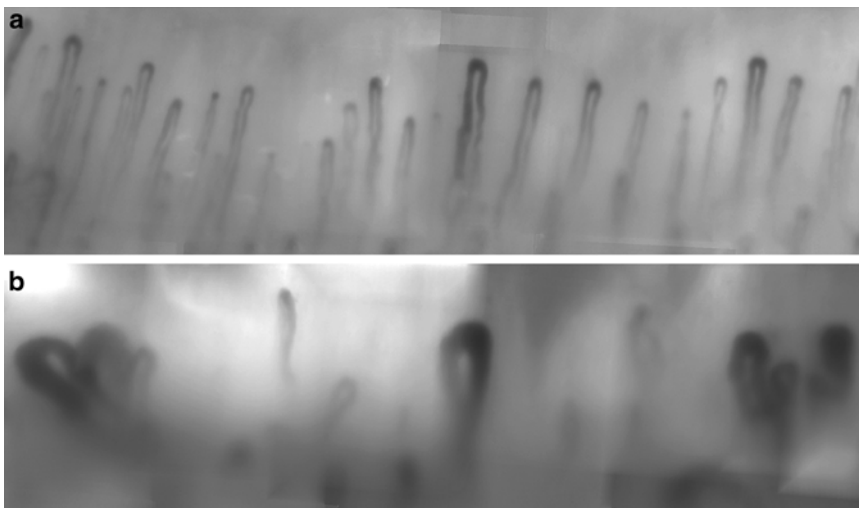


Fig. 6.2 Normal nailfold capillaries (a) compared to abnormal dilated capillaries in a patient with SSc, with areas of avascularity (b)

her final year at university and she has a number of examinations coming up.

Definition

When RP is “primary” this means that it is idiopathic (of unknown cause). Importantly for the clinician, there is no underlying disease or condition to which it is secondary, and which might require specific treatment.

Allen and Brown in 1932 [4] discussed criteria for what was then termed “Raynaud’s disease”. More recent criteria proposed by LeRoy and Medsger in 1982 [5] (already discussed in Chap. 2) are summarised in Table 6.1, and are worthwhile considering in turn, because these highlight a number of key features relevant to the history, examination, and investigation plan:

Episodic attacks of acral pallor or cyanosis: RP attacks are intermittent and resolve. This is usually true also for secondary RP, and so this criterion does not discriminate between PRP and secondary RP.

Strong and symmetric peripheral pulses: This helps to discriminate PRP from RP secondary to structural disease of large arteries, for example atherosclerosis or thromboangiitis obliterans (Buerger’s disease). However, this finding will not discriminate between PRP and RP secondary to SSc-spectrum disorders, nor to several other causes discussed in Chap. 10, when the problem lies primarily in the microcirculation and/or in intravascular factors (for example RP secondary to hyperviscosity syndromes).

No evidence of digital pitting (Fig. 6.3), ulceration or gangrene: This is a key point: by definition if a patient has progressed to irreversible tissue injury then this is not PRP and a secondary cause, for example SSc, *must* be looked for. It should be noted that (in contrast) the Allen and Brown criteria [4] included “gangrene or trophic changes limited in a large degree to the skin” and so could have included digital ulcers and scars

Table 6.1 Proposed criteria for primary Raynaud’s phenomenon [5]

Episodic attacks of acral pallor or cyanosis
Strong and symmetric peripheral pulses
No evidence of digital pitting, ulceration or gangrene
Normal nailfold capillaries
Negative antinuclear antibody (ANA) test (titre <1/100)
Normal erythrocyte sedimentation rate (ESR)



Fig. 6.3 Digital pitting in a patient with SSc. Copyright Salford Royal NHS Foundation Trust

which are now considered by most clinicians to be indicative of underlying disease.

Normal nailfold capillaries: As discussed later, abnormal nailfold capillaries are predictive of a SSc-spectrum disorder.

Negative antinuclear ANA test (titre <1/100): A positive ANA is of concern, as this associates with connective tissue disease, especially when present in a high titre.

Normal ESR: Many secondary causes of RP, including connective tissue disease, malignancy and haematological disorders including diseases associated with hyperviscosity are associated with a raised ESR. A raised ESR demands an explanation.

It is worth mentioning that the criteria of LeRoy and Medsger [5] were a proposal: the diagnosis of PRP is not straightforward as discussed below under “transition”. An example of one of the challenges for clinicians is the definition of “normal nailfold capillaries”, as discussed in Chap. 12 and below under “investigation”.

Epidemiology

As already stated, PRP is very common. Women are more often affected than men. A detailed description of incidence and prevalence is given in Chap. 3. Community based studies which are questionnaire based usually do not include checking of all the parameters listed in Table 6.1 and will therefore most likely include some patients (for example) with abnormal nailfold capillaries or a positive ANA. However, pragmatically most individuals with RP who are not aware that they have an underlying causal disease/condition will have PRP.

Estimates of prevalence of PRP vary widely, as discussed in Chap. 3. To take two examples, a UK community study reported prevalences of RP of 19 % in patients attending surgeries and of 15 % in patients responding to a postal survey: attending surgeries, 21 % women and 16 % men affected; postal survey, 19 % women versus 11 % men affected [6]. A United States community-based study reported prevalences of 11 % in women and 8 % in men [7].

PRP typically presents in the teens or twenties. It is therefore especially important that a secondary cause is excluded when RP develops in older age groups. Children also may present with PRP [8]. The prevalence of RP in 12–15-year-olds has been estimated to be 15 % (18 % in girls, 12 % in boys) [9].

Pathogenesis

The pathogenesis of PRP is not fully understood, although in recent years there have been major advances in our understanding of the cellular and molecular basis of vasospasm, as discussed in Chaps. 4 and 5. The key point to make here is that the episodic imbalance between vasoconstriction and vasodilation which occurs in PRP is thought to be purely *functional*: structural vascular change does not occur. On this basis, abnormal nailfold capillaries exclude a diagnosis of PRP (Table 6.1). Although subtle abnormalities in nailfold capillaries have been reported in PRP [10] this may relate to the fact (discussed below)

that the distinction between PRP and early SSc is not absolute.

The pathophysiology of RP is discussed in full in Chap. 5 and only a few points will be made here. When studying pathophysiology, investigators often compare patients with PRP to patients with SSc-related RP and to healthy controls: when abnormalities are found in patients with PRP, these may be less marked than in patients with SSc-related RP. Abnormalities in patients with PRP include reduced endothelium-dependent vasodilation [11–13], reduced expression in finger skin of the vasodilator calcitonin gene-related peptide [14], increased protein kinase activity and tyrosine phosphorylation [15], platelet activation [16–19], white blood cell activation [20] and oxidative stress [21]. Although some studies have suggested a role for endothelin-1 [22–24] the evidence (as discussed in Chap. 5) is conflicting. Genetic factors have also been implicated in the pathogenesis of PRP [25, 26], as discussed in Chap. 3.

History and Examination

The approach to diagnosis of the patient with suspected or definite RP is summarised in Fig. 6.4. The clinician must differentiate primary from secondary RP, and gauge the severity of the RP because this will inform treatment decisions.

In diagnosing and assessing severity of PRP, the key points in the history are:

1. The typical colour changes of the fingers and toes (usually in response to cold exposure or emotional stress). Classically the fingers turn white (ischaemia), then blue (deoxygenation) then red (reperfusion), although many patients report only a uniphasic or biphasic response (including white or blue). The colour changes are confined to distal to the metacarpophalangeal joints, and can last variable lengths of time, but in patients with PRP usually resolve quickly (within minutes) after rewarming. Patients often report cold sensitivity rather than colour change of the feet which are less visible. The nose, ears and nipples [27] may also be affected (Fig. 6.5). Although attacks tend to be symmetrical, some fingers may be

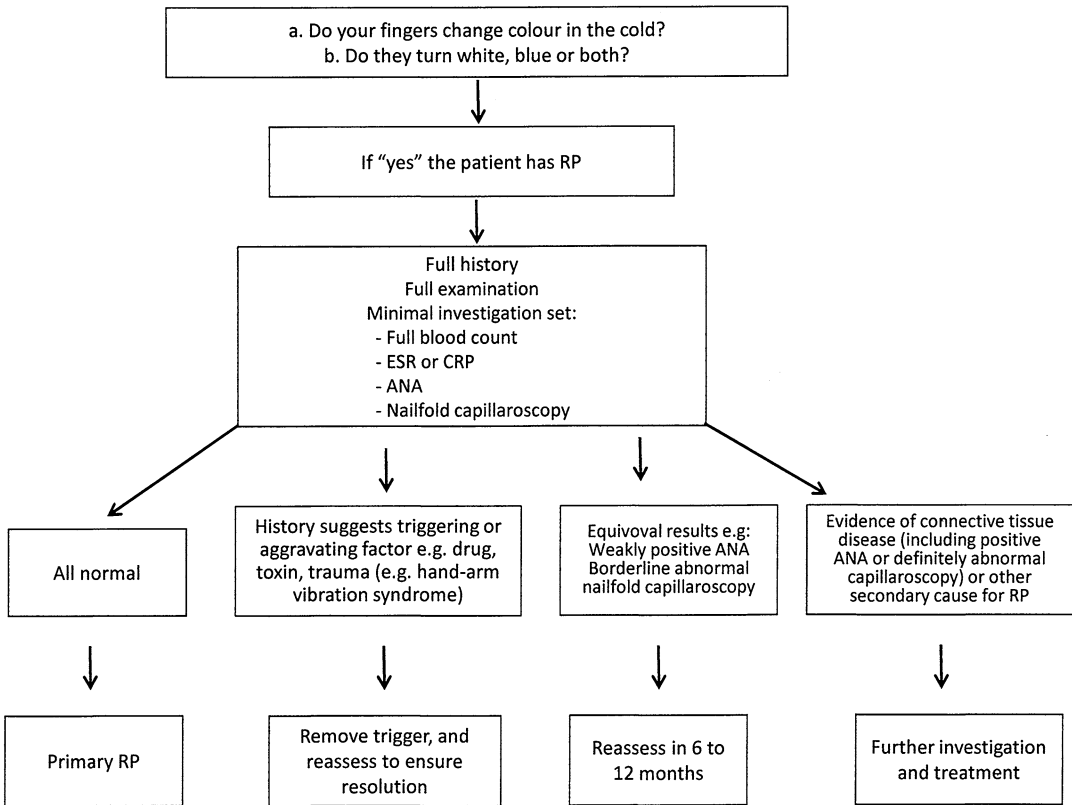


Fig. 6.4 Flow chart summarising the approach to diagnosis of RP

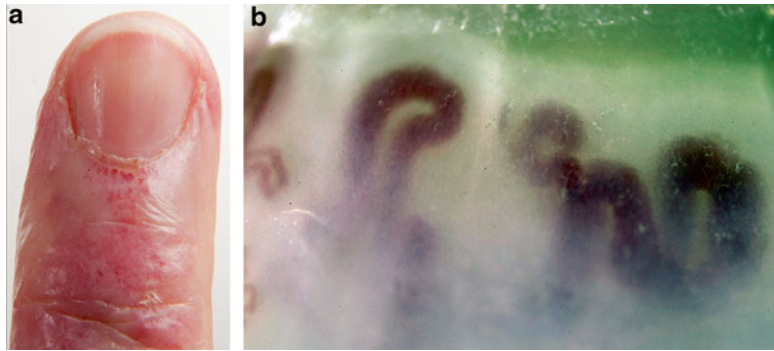


Fig. 6.5 Cartoon of the “cold skin zones” in healthy control subjects (fingers, hands, toes, feet, knees, nose, ears): these are exaggerated in patients with PRP

more affected than others. The thumbs are often spared, and if affected then this should prompt the clinician to be especially careful to exclude an underlying connective tissue disease [28]. It is worth highlighting that many people are cold sensitive, but for a diagnosis of RP, there must be colour change (Fig. 6.4).

2. Absence of any symptoms suggestive of a connective tissue disease or of any of the other causes of secondary RP (Table 3.2). Therefore, it is essential to take a comprehensive history including a full systems enquiry (connective tissue disease can present with a wide range of symptoms, e.g. recent onset of heartburn could suggest oesophageal dysmotility), drug history, social history (with full occupational history including vibratory tool exposure, industrial chemical exposure) and family history (many patients with PRP have a family history of RP).
3. Assessment of severity. Are the attacks painful and interfering with activities of everyday living?

Fig. 6.6 Nailfold capillaries that were so dilated as to be visible to the naked eye (a) and as shown by capillaroscopy (b). This patient had dermatomyositis. Courtesy of H Chinoy. Copyright Salford Royal NHS Foundation Trust



On examination, the fingers and face should be carefully examined for sclerodactyly, digital pitting, digital ulcers, calcinosis, periungal erythema, telangiectases, and any capillary dilation or haemorrhages (at the nailbed) which are so marked as to be visible to the naked eye (Fig. 6.6). The peripheral pulses must be checked. A full examination is required for the same reason as a full history (e.g. basal crackles might indicate connective tissue disease-associated interstitial lung disease).

Investigations

As directed by the criteria for PRP (Table 6.1), the basic set of investigations comprises a full blood count, ESR, ANA and nailfold capillaroscopy (Fig. 6.4). Many clinicians would also include a biochemical profile with thyroid function tests and (especially if symptoms are unilateral) a thoracic outlet radiograph to look for a cervical rib (Fig. 6.7). All should be normal in the patient with PRP.

Many clinicians do not have access to nailfold videocapillaroscopy, which is the “gold standard” capillaroscopy technique (Chap. 12). A lower magnification technique should then be used: a stereomicroscope, dermatoscope [29, 30] or ophthalmoscope [31, 32]. There has been recent increased interest in the dermatoscope, which is a small portable hand-held piece of equipment which can be used in the office or outpatient clinic [33]. An advantage of lower magnification is that the whole nailbed is included in



Fig. 6.7 Bilateral cervical ribs

one field of view, although it is likely that more subtle abnormalities seen with high magnification videocapillaroscopy are missed. Figure 6.8 shows example images using the dermatoscope and videocapillaroscopy.

It is worth highlighting that the interpretation of nailfold capillaroscopy images can be difficult. As discussed in Chap. 12, there is a wide range of “normality”: healthy controls do not all have evenly shaped “hairpin” loops (Fig. 6.2a) but can have considerable tortuosity of their capillaries. Figure 6.9 shows examples of capillary appearances which are not definitely “scleroderma-spectrum” but which nonetheless are not entirely normal. Also, it is not always possible to visualise everyone’s capillaries and this should not be mistaken for avascularity. However, definite abnormalities of a systemic

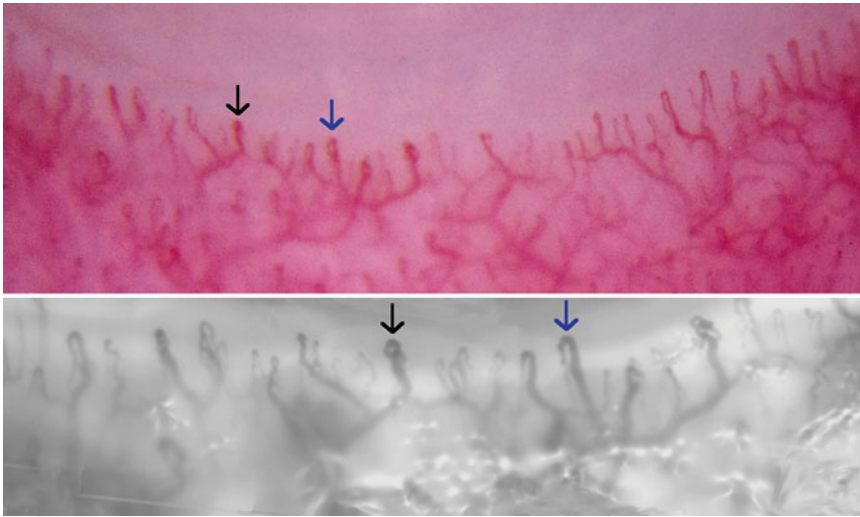


Fig. 6.8 Normal capillaries in a patient with PRP, imaged with a dermatoscope (*top*) and videomicroscope (*bottom*). The *arrows* indicate the position of the same capillaries

using each technique. The higher magnification gives more detailed visualisation of the individual capillaries

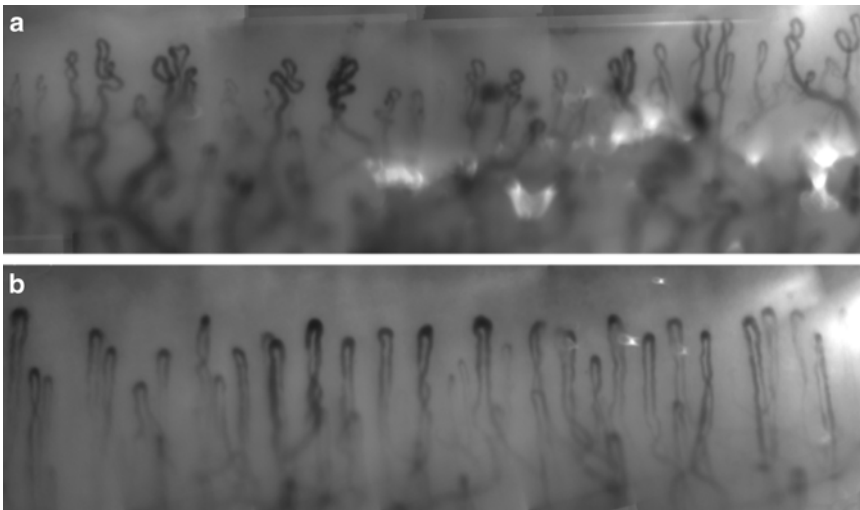


Fig. 6.9 Nailfold capillaries in healthy control subjects showing (a) marked tortuosity (b) regular capillaries but with some variation in apical diameters. These images demonstrate the challenges in defining “normality”

sclerosis-spectrum disorder, for example giant capillaries, are not consistent with a diagnosis of PRP (Chap. 12).

Thermography, which measures surface temperature (Chap. 13), can help to differentiate primary from secondary RP, but is available only in certain specialist centres. Most thermography protocols will include a temperature

challenge (Fig. 6.10), usually a cold challenge [34–36].

A number of other methodologies which are used in research studies can help to distinguish between PRP and SSc-associated RP. These include laser Doppler flowmetry, laser Doppler imaging, finger systolic pressure measurement and plethysmography. They are discussed in Chap. 13.

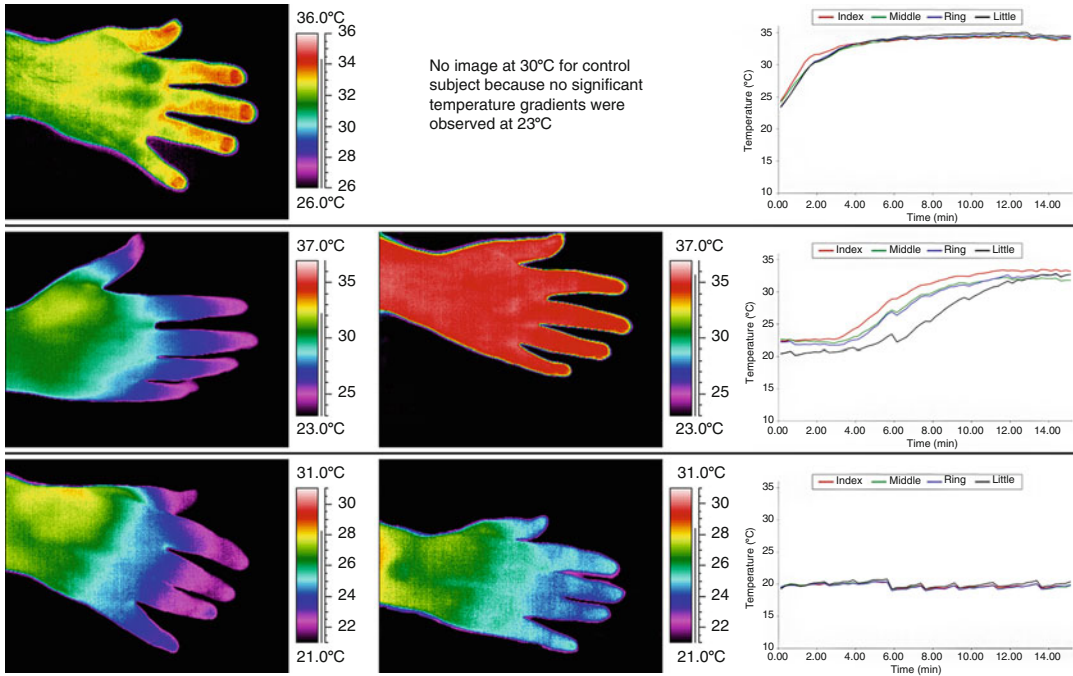


Fig. 6.10 Thermograms from a healthy control subject (*upper*), a patient with PRP (*middle*) and a patient with SSc (*lower*). The thermograms on the left are at 23 °C, and on the right at 30 °C. Although in both patients the fingertips are cold at 23 °C, this temperature gradient along the fingers normalises at 30 °C in the patient with

PRP, but not in the patient with SSc (suggesting underlying structural vascular disease). The rewarming curves on the right show rapid rewarming in the healthy control subject, delayed (but complete) rewarming in the patient with PRP, and no rewarming within the 15 min observation period in the patient with SSc

Treatment

Many patients with PRP do not even seek medical advice, and most do not require drug treatment. Once the diagnosis of PRP is made, a key point is to reassure that patient that there is no evidence of any underlying condition, and that the aim of treatment is to minimise symptoms. Treatment of RP is discussed in detail in Chaps. 19 and 20, but some general points especially relevant to PRP will be made here.

Patient Education/General Measures

This is probably the most important aspect of management, discussed in Chap. 19. Patients should be advised to minimise the impact of

changes in temperature by dressing warmly (not only warm socks, gloves and hats but also keeping centrally warm). Many patients use hand-warmers, and some find electrically heated gloves and socks helpful. Leaflets describing RP and ways to keep warm are published by patient support groups (Fig. 6.11).

If patients smoke, they should be advised to stop. Of interest is that a survey in the Framingham Heart Study Offspring Cohort suggested an association between current smoking and Raynaud's phenomenon in men (adjusted Odds ratio 2.59, 95 % confidence interval 1.11–6.04) but not in women [37], consistent with findings of an earlier study [38].

In many patients with PRP, symptoms improve over time [7, 39], possibly at least in part because patients become less concerned about them, or make lifestyle modifications which prevent attacks.



Fig. 6.11 Examples of patient education leaflets. Copyright Salford Royal NHS Foundation Trust

Drug Treatment (Table 6.2)

This should be considered in the patient who does not respond to general measures and is discussed in detail in Chap. 20.

Most clinicians recommend calcium channel blockers [40] as their first choice, although adverse effects are common, including vasodilatory side effects such as headache, flushing and dizziness. Sustained release preparations tend to be better tolerated, and a key point is to commence at low dosage and gradually increase. Despite the widespread use of calcium channel blockers in PRP, these were reported to be only minimally effective in a recent Cochrane review [41] which included seven randomised trials (four examining nifedipine, three nifedipine) and 296 patients. Overall, the number of RP attacks per week was reduced by 1.72 (95 % CI 0.60–2.84) meaning that calcium channel blockers could reduce the weekly number of attacks by as few as 0.6 or as many as 2.8 [41].

Table 6.2 Drugs used in the patient with PRP, in whom general (“non-drug”) measures are insufficient to control symptoms

Calcium channel blockers (e.g. nifedipine, amlodipine) ^a
Angiotensin II receptor antagonists (e.g. losartan).
Angiotensin-converting enzyme inhibitors
Alpha-adrenergic blockers (e.g. prazosin)
Serotonin reuptake inhibitors (e.g. fluoxetine)
Phosphodiesterase inhibitors (e.g. sildenafil)
Topical nitrate therapy (this causes both systemic and local vasodilation—doses used for systemic effects are often poorly tolerated, and at present there is no licensed formulation available for local application)
Intravenous prostanoids (seldom used for PRP)

^aFirst line treatment

There is even less evidence base to support the use of any other class of drug in patients with PRP, as discussed in two other recent reviews [42, 43]. This lack of evidence base is due at least in part to the difficulties in mounting clinical trials of RP. However, it seems reasonable, if a calcium channel blocker is ineffective or not tolerated, to

prescribe an alternative vasodilator. Other drugs used in the treatment of PRP include angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors and alpha-adrenergic blockers (Table 6.2). Phosphodiesterase inhibitors are being prescribed increasingly, at present more for secondary than for primary RP. To date there has been very little research into the effects of phosphodiesterase inhibitors in patients with PRP: one study in 15 patients with PRP suggested that a single dose of 100 mg sildenafil improved finger blood flow during local cooling [44]. Topical glyceryl trinitrate (GTN, nitroglycerine), applied locally to the fingers has recently been revisited in a clinical trial including both patients with PRP and with SSc-related RP [45], but at present there are no formulations available specifically for applying to the fingers in patients with RP (this is an area requiring further research). When GTN is given by transdermal patch for its systemic effects [46], it tends to be poorly tolerated and is therefore seldom used, although a recent report suggested that this was useful in childhood RP [47]. Intravenous iloprost is occasionally prescribed for patients in whom PRP attacks are particularly severe, but this treatment is generally reserved for patients with secondary RP, progressing to digital ulceration.

A challenge to clinicians is the patient with PRP and a low blood pressure, intolerant of vasodilator preparations. General (non-drug measures) should be revisited. Some clinicians try a selective serotonin reuptake inhibitor [48] which may be better tolerated than the therapies already mentioned.

Treatment efficacy in primary versus secondary RP: Some clinical trials have included patients with both PRP and SSc-related RP and compared treatment effect between subgroups. The caveats of subgroup analysis, discussed in Chap. 18, should be borne in mind. Given that the evidence base for treatment of both PRP and secondary RP [49] is weak, in general it is usually difficult to say whether treatment effect is greater or less in patients with PRP. However, it might be reasonable to assume that patients with PRP are more likely to respond to vasodilator therapy than patients with SSc-related RP, because they do not have structural vascular disease. This is borne out

by some studies which suggest greater efficacy in PRP than in SSc-related RP, for example the study by Chung et al. [45] of topical GTN, which included 69 patients with PRP and 150 with secondary RP (131 of whom has SSc), and studies of fluoxetine [48] and losartan [50].

Other Treatments

Although botulinum toxin has been recommended for primary as well as secondary RP [51], there is no good evidence base for this approach. There is no role for surgery in the treatment of PRP.

Transition from Primary to Secondary RP

This is a difficult area and has already been referred to in Chap. 3. The literature suggests in the order of 1–3 % of patients per year with what appears to be PRP or “isolated” RP progress to SSc or other underlying disease [52, 53]. A key issue is how carefully RP is “vetted” before classed as primary. A study which followed 586 patients with RP over 3,197 patient years (median follow-up 4 years) reported rates of progression to SSc as follows [54]: 1.8 % of patients with neither an abnormal nailfold capillary pattern nor a SSc-specific autoantibody; 25.8 % of patients with an abnormal nailfold capillary pattern; 35.4 % of patients with a SSc-specific autoantibody; 79.5 % of patients with both an abnormal nailfold capillary pattern and a SSc-specific autoantibody. Another level of complexity is the definition of transition. For example, Cutolo et al. [55] reported that 14.6 % of 129 patients with PRP (normal nailfold capillaries, ANA negative) developed abnormal nailfold capillary patterns over a mean of 29.4 months. The conclusion must be that the separation between PRP and early connective tissue disease-associated RP is not absolute, and that abnormal nailfold capillaries and SSc-specific autoantibodies (although not diagnostic in themselves) are “red flags”. This has been acknowledged in the American

College of Rheumatology/European League Against Rheumatism 2013 classification criteria for SSc [56, 57], which include both abnormal capillaroscopy and SSc-specific autoantibodies.

If the clinician is unsure, for example a patient has a positive ANA of 1/100 and equivocal nailfold capillaroscopy (e.g. normal architecture, but one or two areas of haemorrhage, or some borderline widened capillaries) then the pragmatic approach is to review the patient and repeat the capillaroscopy 6–12 months later (Fig. 6.4).

Expert Opinion

PRP is common, and does not progress to irreversible tissue injury. An important aspect of management is to make the correct diagnosis (i.e. not miss a secondary cause) and then reassure the patient accordingly. A patient with PRP should have no worrying features on history and examination and investigations (full blood count, ESR, ANA and nailfold capillaroscopy) should all be normal.

Many patients with PRP will respond to reassurance and general (non-drug) measures: in those with persisting symptoms requiring drug treatment, a calcium channel blocker (sustained release) is generally the first choice, starting at low dosage and gradually increased as tolerated and indicated. If the maximum tolerated dose is ineffective, an alternative vasodilator should be tried.

In the research setting, comparing patients with PRP to those with SSc-related RP may help to elucidate why patients with SSc, but not those with PRP, may progress to digital ulceration and critical ischaemia.

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