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Iatrogenic Raynaud phenomenon: a systematic review and a network meta-analysis of peripheral vasoconstriction induced by beta-blockers

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FACULTE DE PHARMACIE DE GRENOBLE

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MEMOIRE DU DIPLOME D'ETUDES SPECIALISEES DE
PHARMACIE HOSPITALIERE - PRATIQUE ET RECHERCHE

Conformément aux dispositions du décret N°90-810 du 10 septembre 1990 tient lieu de

THESE

LE PHENOMENE DE RAYNAUD IATROGENE : REVUE DE LA LITTERATURE
ET META ANALYSE EN RESEAU DES VASOCONSTRICTIONS PERIPHERIQUES
INDUITES PAR LES BETA-BLOQUANTS.

Présentée à la Faculté de Pharmacie de GRENOBLE
Et soutenue publiquement le : 03 juillet 2015
Pour obtenir le grade de DOCTEUR EN PHARMACIE

Par :

M. Charles Khouri

[Données à caractère personnel]

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Résumé

Le phénomène de Raynaud (RP) iatrogène est une entité mal connue, représentant pourtant une des principales étiologies de RP secondaire. Afin de synthétiser les connaissances sur le sujet nous avons réalisé une revue systématique de la littérature. L'approche mécanistique utilisée nous a permis de mettre en évidence quatre voies physiopathologiques principales. Les données sont malheureusement peu fiables dans la majorité des cas et de nombreuses questions demeurent quant à la prévalence, la présentation clinique et le traitement de ces PR médicamenteux. Nous avons ensuite réalisé une méta-analyse en réseau dans le but de déterminer la prévalence des vasoconstrictions périphériques (PV) chez les patients prenant des bêta-bloquants et de mettre en évidence, une possible différence entre chaque type de bêta-bloquant. Il ressort de cette étude une augmentation significative du risque de PV ainsi qu'une hétérogénéité importante au sein de cette classe. Ces observations remettent en cause la pertinence des contre-indications de certains bêta-bloquants chez les patients atteints de PR.

Abstract

Drug-induced Raynaud's phenomenon (RP) has long been associated with the use of different classes, but its prevalence remains largely unknown. In order to synthesize available knowledge on this topic we conducted a systematic review, by using a mechanistic approach. We identified many drug classes and four main pathophysiological pathways. However, the level of evidence was poor in most cases and many questions remain. We then focalized on the example of beta-blockers and performed a network meta-analysis (NMA). This NMA aimed at assessing the prevalence of peripheral vasoconstrictions (PV) in patients taking beta-blockers and to explore the potential differences among beta-blockers. Our study reveals important heterogeneity among beta-blockers, with a protective effect of intrinsic sympathomimetic activity as compared with β_1 -adrenoceptors higher affinity. These results challenge recommendations on the use of beta-blockers in patients presenting RP and PV.

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LECA : Laboratoire d'Ecologie Alpine

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LISTE DES ABREVIATIONS

ACE: Angiotensin-converting enzyme inhibitors

ADHD: Attention deficit hyperactivity disorder

ARB: Angiotensin II Receptor Blockers

CCB: Calcium Chanel Blocker

GRADE: Grading of Recommendation Assessment, Development and Evaluation

IFN: Interferons

ISA: Intrinsic sympathomimetic activity

MSA: Membrane-stabilising activity

NMA : Network méta analysis ; méta analyse en réseau.

OR: Odds Ratio

PV: Peripheral vasoconstriction ; vasoconstriction périphérique

RP: Raynaud phenomenon ; phénomène de Raynaud

SSc: Systemic sclerosis

SSRIs: Selective serotonin-reuptake inhibitors

TD: Thiazide diuretic

VB: Variceal bleeding

INTRODUCTION

Le phénomène décrit pour la première fois par Maurice Raynaud en 1862 comme une « asphyxie des extrémités » est la traduction clinique d'une vasoconstriction paroxystique des extrémités, en réponse à un stress environnemental (froid, plus rarement humidité) ou émotionnel. Le phénomène de Raynaud (RP) se traduit cliniquement par 3 phases accompagnées d'un changement de couleur des doigts. La phase de vasoconstriction excessive où les doigts sont blancs, la phase de cyanose tissulaire où ils sont bleus, et enfin la phase de reperfusion hyperémique rouge, souvent douloureuse. Ces trois phases ne sont pas systématiquement observées chez un même patient et ne sont pas indispensables au diagnostic. La durée d'un épisode varie de quelques minutes à plusieurs heures.

Le RP idiopathique ou primaire, souvent bénin et sujet à des variations géographiques importantes, touche 4 à 6 % de la population générale avec une prévalence supérieure chez les femmes (jusqu'à 20 %). Plus rarement le RP peut être secondaire à certaines pathologies altérant la microcirculation périphérique, il peut alors donner lieu à des complications plus graves et induire ulcérations digitales et gangrènes. Les connectivites (sclérodémie systémique, lupus érythémateux disséminé..), les vascularites, une compression vasculaire, une artériopathie, des pathologies induisant une hyperviscosité sanguine ou encore certains médicaments peuvent être des causes de PR secondaires.

La physiopathologie du PR est multifactorielle, complexe et encore imparfaitement connue à ce jour. Les mécanismes impliqués sont nombreux et la part de chacun varie en fonction de l'étiologie de la maladie. L'origine iatrogène du PR est décrite depuis plusieurs décennies, initialement avec l'utilisation de composés de type chlorure de vinyle puis avec l'avènement des premiers bêta-bloquants dans les années 1970. Elle représente une des principales

étiologies de RP secondaire, probablement sous-estimée en raison de la faible connaissance de cet effet indésirable. De multiples classes médicamenteuses sont soupçonnées d'aggraver ou d'induire un PR. Nous nous proposons donc ici d'en faire tout d'abord une revue de la littérature (Article 1), approfondissement d'un précédent travail sur la pharmacologie du RP (Annexe1).

Dans un second temps nous nous focaliserons sur ce que nous appellerons plus largement vasoconstrictions périphériques (PV) qui englobent les acrosyndromes et RP induits par les bêta-bloquants. Cette classe médicamenteuse est reliée depuis de nombreuses années à l'apparition de PV, d'où la contre-indication de la plupart des bêta-bloquants chez les patients porteurs de RP en France. Plusieurs questions subsistent pourtant encore à l'heure actuelle. Nous n'avons que très peu de données fiables sur la prévalence de RP chez les patients prenant des bêta bloquants et encore moins sur une possible différence entre chaque type de bêtabloquant. Au sein de cette classe, il existe une grande hétérogénéité pharmacologique à même de modifier la capacité de chaque bêta-bloquant d'induire des PV. Cette différence n'a pourtant jamais été mise en évidence avec certitude. Paradoxalement, un grand nombre d'essais cliniques impliquant des bêta-bloquant ont été publiés dans la littérature depuis les années 1960. Il doit donc être possible d'utiliser ces données afin de hiérarchiser le risque de PV en fonction du type de propriétés pharmacologiques secondaires de chaque bêta-bloquant et ainsi de rationaliser leurs précautions d'emplois. Pour répondre à cette question nous avons réalisé une revue systématique de la littérature et une méta analyse en réseau de ces essais cliniques (article 2).

Drug-induced Raynaud's phenomenon

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Introduction

Raynaud's phenomenon (RP) is characterized by transient ischemia of the extremities in response to environmental stress or emotions (1). It typically manifests as changes of the fingers, with pallor (vasospasm and decreased blood flow), cyanosis (deoxygenation of the static venous blood), and rubor (reperfusion), often accompanied by pain. RP can be primary (i.e. idiopathic) or secondary to an underlying cause. In both cases, cutaneous microcirculatory abnormalities are primarily involved in the pathophysiology of RP (2).

The prevalence of RP in the general population varies between 0.5 and 19%, with major geographic variability (3–6). While primary RP is the most frequent form (80-90%) (7), RP may also be secondary to various auto-immune diseases (such as systemic sclerosis (SSc), systemic lupus erythematosus, vasculitis, etc), malignancies, atherosclerosis or hypothyroidism (1). Several drugs with peripheral vascular effects leading to decreased microvascular perfusion may induce or aggravate RP; drug-induced RP are probably underestimated because of the limited knowledge of this side effect.

Literature reviews and textbooks usually mention drugs that have long been known to be responsible for RP. However, new signals are emerging from numerous cases reports. Yet, to our knowledge, no systematic review has been performed and little is known about the prevalence and the level of evidence of drug-induced RP. Our objective in the present work was therefore to summarize available evidence and to propose a mechanistic approach of drug-induced RP.

Methods

The MEDLINE database was searched for English or French language papers published between January 1946 and May 2015 using the following search terms: "Raynaud Disease/chemically induced"[MESH] and "raynaud\$" AND "clonidine", "betablocker", "ergot

alkaloid”, “dopaminergic agonist”, “Selective serotonin-reuptake inhibitors”, “Sympathomimetic drugs”, “chemotherapy”, “Tyrosine kinase inhibitors”, “interferon”, “cyclosporine”. Further relevant papers were identified from the reference lists of retrieved articles.

Results

1. Drugs enhancing vasoconstriction

1.1. Clonidine

RP induced by clonidine is a well-known side effect, described such many years although its frequency is not known (8). Clonidine exerts peripheral vasoconstriction through α_2 -adrenoceptor agonism, which has been suggested to be a major etiologic mechanism of non-iatrogenic RP (1,9). Of note, skin vasoconstriction in response to local cooling is mediated by the translocation of α_{2c} -adrenoceptors to the vascular smooth muscle cells surface, through a pathway involving RhoA–Rho kinase (10). Because cold-amplified α_2 -adrenoceptor constrictive activity is increased in patients with RP (9,11), clonidine may potentiate the effect of cold on the occurrence of RP.

1.2. Beta-blockers

Beta-blockers are a long known cause for drug-induced RP, but data about its prevalence are scarce. Analyze of the Framingham Heart study identified beta-blockers use as the most common cause of secondary RP (34.2% of secondary RP). A meta-analysis published in 2012 that included 13 studies (1012 patients), found a prevalence of 14.7% in patients receiving beta-blockers (4). However, studies were old (1971 to 1984) and of varying quality. A network meta-analysis of prospective, randomized controlled trials reveals a prevalence of peripheral vasoconstriction among patients treated with beta-blockers of 7%

(1966/28072), whereas 4.6% (555/12060) and 1.7% (305/17492) of patients treated with placebo or active control experienced this adverse effect, respectively ($P < 0.001$) (Article 2).

The pathophysiology of this side effect remains unclear. Studies exploring the effect of beta-blockers on patients with a primary RP failed to show any worsening of their symptoms (12–15). There is no evident explanation for this discrepancy, but studies are small sample sized.

The influence of ancillary properties of beta-blockers (e.g intrinsic sympathomimetic activity, β_1 -selectivity, vasodilator activity) should theoretically influence their propensity to induce peripheral vasoconstriction, although studies report conflicting results (15–18). The recent network meta-analysis conducted by our group suggests that the vasoconstrictor sympathetic reflex mediated by baroreceptors in response to the decreased cardiac output would be involved, rather than a direct vasoconstrictor effect mediated through β_2 -adrenoceptors (Article 2).

1.3. Ergot alkaloids

Ergotamine and derivatives are used to treat migraine disorders and cluster headache (19). They display affinity for a wide variety of receptors including those for 5-HT (serotonin), dopamine, and noradrenaline. (20) They are partial agonist at various serotonergic receptors and the classical response of blood vessels to 5-HT is contraction (21). More precisely, they exert central vasoconstrictor effect through serotonergic 5-HT_{1B/1D} receptors, which are mostly in the cranial vessels and at therapeutic dose exert only a weak constricting effect on peripheral blood vessels.(22) Indeed, triptans which are selective agonist 5-HT_{1B/1D} are not known to induce PV and RP. However 5-HT₂agonism seems to be the main effector of their peripheral serotonergic vasoconstrictor effect. Moreover, they are α_1 , α_2 adrenergic and dopaminergic D₂ agonist. Numerous case reports illustrating this effect

are found in the literature (23,24). However, accountability of ergot alkaloids in RP is difficult to assess because of a significantly higher prevalence of RP in migraine population (25,26). Furthermore, the peripheral vascular manifestations of ergot alkaloids are sometimes interpreted as a RP. Although it is rarely observed (its estimated incidence is 0.1%). “Ergotism” rather manifests as prolonged vasoconstriction that may lead to gangrene.

1.4. Dopaminergic agonists

Some RP cases were exceptionally reported with the use of bromocriptine, which is also an ergot alkaloid (27–30). One case describes a severe RP with a vascular morphological injury (presence of megacapillary on nailfold capillaroscopy) attributed to a 6 years treatment by bromocriptine(29). Supposed pathophysiology of RP induced by bromocriptine is dopaminergic D2 agonism, leading to peripheral release of catecholamines resulting in vasoconstriction. Direct activation of α_2 -adrenoceptor receptors by bromocriptine has been described in pancreatic cells (31) and could explain increased sensitivity to cold during bromocriptine therapy. Microvascular injury with long term use of bromocriptine has also been suspected (29). Of note, a large case-control study (542 cases and 2155 controls) did not support an association between dopamine agonists and an increased risk of ischemic events requiring hospitalization (32). However this study does not provide detailed information on RP.

1.5. Selective serotonin-reuptake inhibitors (SSRIs)

Contradictory effects of SSRIs on peripheral vasoreactivity were observed. Indeed on one side, SSRIs were proposed as a treatment of RP (33), following observation of patients with erythromelalgia or RP relief with fluoxetine and sertraline (34), paroxetine and escitalopram(35). On the other hand, observations suggested a positive link between RP and SSRIs: fluoxetine (36,37), fluvoxamine (38), citalopram (39), milnacipran (40); and with the

relief of erythromelalgia symptoms (41). The case of an emerging RP two days after beginning a tergaserod treatment, a partial 5-HT₄ serotonin receptor agonist, has also been described (42).

Currently this discrepancy remains unexplained. Some authors suggested that endothelium damage is necessary for the development of a vasoconstrictive effect during SSRI treatment (43). In healthy vascular bed, it has been suggested that blocking serotonin reuptake could increase free plasma serotonin concentration and produce, in stasis conditions, a local serotonin accumulation, exacerbating a vasoconstriction through 5-HT₂ receptors that may worsen RP (39). Individual variability in metabolism or in signaling serotonin pathways could also explain the variability in response to SSRIs (33).

1.6. Stimulants

Central stimulation of the dopaminergic and noradrenergic system is responsible for the peripheral release of catecholamines leading to vasoconstriction. Cases of RP induced by central nervous system stimulants have been reported (44). A retrospective case-control study has investigated whether medications used for the treatment of attention deficit hyperactivity disorder (ADHD) were associated with the development of RP. Sixty-four children were enrolled in the study (32 cases with RP and 32 ages and sex matched control patients) and a significant association between the presence of RP and past or current use of ADHD stimulants (methylphenidate and dextroamphetamine) were found (45). Atomoxetine, a selective noradrenaline reuptake inhibitor, were excluding of this study because it wasn't considered as a central nervous system stimulant. However the case of a dose dependent RP emerging from the use of atomoxetine on a girl has recently been described (46). And two other cases of reboxetin, an inhibitor of noradrenalin reuptake, were also described(42). Amphetamine-like drugs had also been associated with emergence of RP and vasculopathy.

Like phentermine, a weak sympathomimetic agent, used most commonly as an appetite suppressant in the treatment of obesity(47).

1.7. Sympathomimetics

A digital necrosis was described with the local use of lidocaine/epinephrine in a patient with primary RP (48). In the same way, there are limited data about sympathomimetic nasal decongestants (pseudoephedrine, phenylephrine). However, the pharmacologic properties of these drugs and their poor clinical benefit led to contraindicate them in patients with scleroderma-related RP (49).

Among non-medical drugs, cocaine abuse was related to RP with ischemic finger necrosis in a 37-year-old man (50). Cocaine has a potent vasoconstrictor effect through an α_2 -adrenoceptor activity. It has also been shown to alter prostaglandin production with disproportionate increases in thromboxane in rabbit endothelium, with the consequences of vasospasm, platelet activation and thrombus formation(51,52). Although in some cases cocaine may induce RP, it is more likely to be the consequence of a Buerger-like syndrome (53–55), as described with cannabis use (56,57).

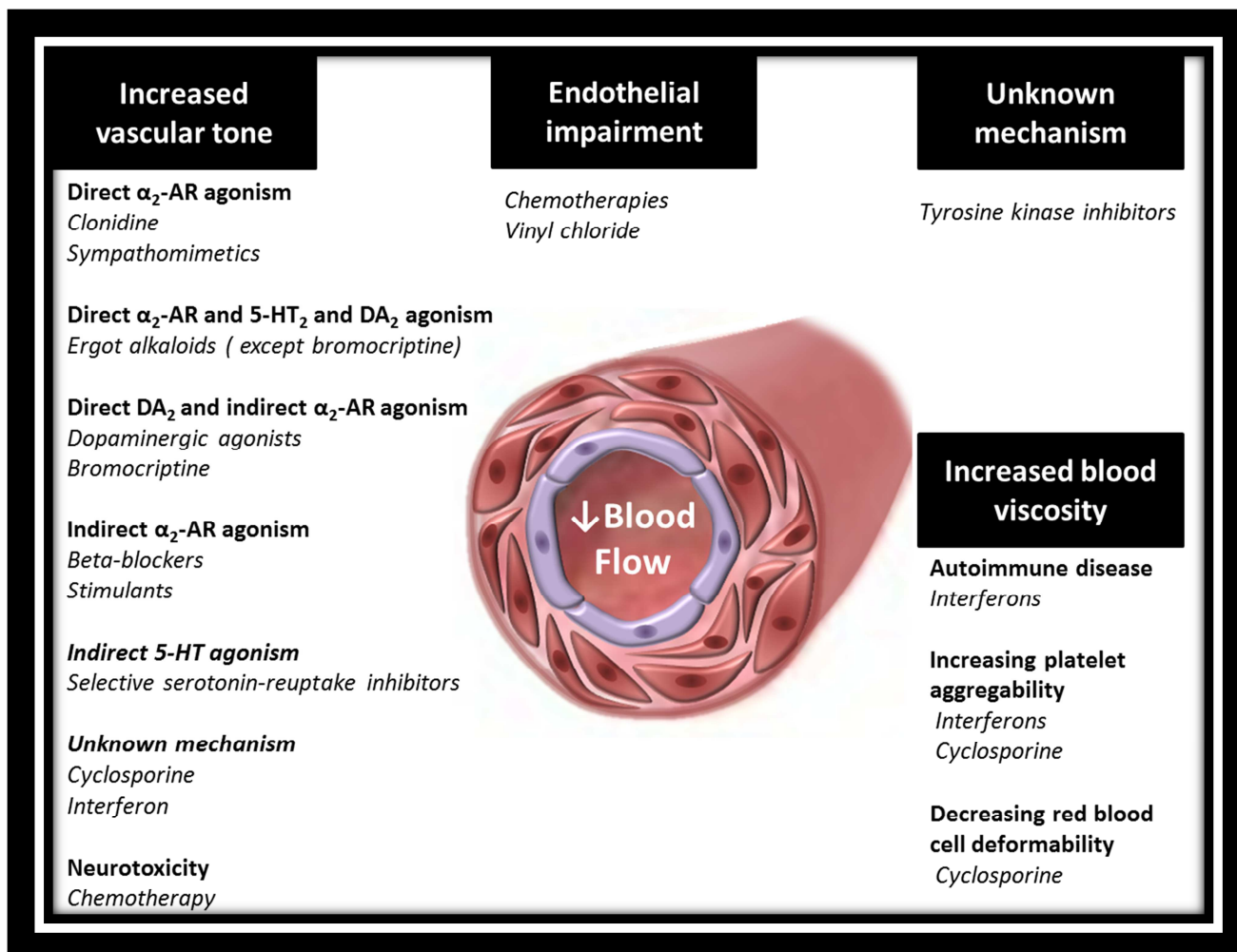


Figure 2. Schematic representation of some of the key mechanisms contributing to the pathogenesis of iatrogenic Raynaud phenomenon

2. Drugs damaging the endothelium

2.1. Cancer chemotherapies

The link between RP and chemotherapies has been identified a long time ago. First descriptions of chemotherapy-induced RP were related to testicular cancer treatments (58–60). A 1995 study including 90 patients treated with cisplatin-based chemotherapy for more than 1 year after testicular cancer therapy found that 37% of them had developed RP after four cycles of chemotherapies combining cisplatin, bleomycin and vinblastine (61). RP typically appears 3 to 6 months after chemotherapy starts, and often persists for several years (62). Identified risk factors for the development of RP in this study were high cumulative dose of bleomycin and association of bleomycin with vinblastine rather than etoposide. Furthermore, a trend for an increased prevalence of RP was observed in patient who received administration of bleomycin as a bolus compared to continuous infusion. No significant correlation was seen with the cumulative or single doses of cisplatin, etoposide or vinblastine, serum magnesium levels during or after chemotherapy or a history of smoking (61)

These results were confirmed by the follow-up of a cohort study including 739 patients treated for a testicular cancer between 1982 and 1992. Patients were divided between chemotherapy (n= 384) and non-chemotherapy (n=355) groups. Prevalence of RP was significantly higher among patient who received chemotherapy (20.7% versus 1.7%; $P<0.001$)(63). Once again, a significant relationship between the cumulative dose of bleomycin and the prevalence of RP was found (OR= 2.98[2.286-3.388]; $P<0,001$). Thirteen percent of patients still suffered of RP 10 years after having received a cumulative bleomycin dose $<180000\text{IU}$ (corresponding approximately to 3 cycles of Cisplatin-Etoposide-Bleomycin), 24.6% after a cumulative dose of 180 000IU to 360 000IU, and 29% for a cumulative dose $>360\ 000\text{IU}$. A large observational study (64) including 1409 testicular

cancer survivors found a prevalence of RP among the chemotherapy group of 39%. These cancer chemotherapy associated vinca alkaloids, cisplatin and bleomycin. The odds ratios for Raynaud-like phenomena who received one to four cycles of chemotherapy compared with those who received no chemotherapy were 2.9 [2.2-3.9], and 8.0 [4.4-14.7] if they received more than 5 cycles of chemotherapy. These drugs were also used for Kaposi's sarcoma treatment and RP was also described (65–69). Nevertheless, emergence of a severe RP with digital necrosis after a single cycle of doxorubicin, bleomycin, vincristine, and dacarbazine chemotherapy, with a cumulative dose of only 40,000 IU of bleomycin has also been described (70). Cases describing the occurrence of RP after local injection of bleomycin to treat wart have also been reported (71–75).

Raynaud's phenomenon has also been associated with cisplatin-based chemotherapies for testicular cancer (76). A recent meta-analysis on cisplatin-based chemotherapies included 24 studies (n=2479 patients) and found a prevalence of RP of 24% (17.5- 31.3) (72). However, cisplatin was almost always associated with bleomycin and vinca alkaloids making it accountability difficult.

Among other cancer chemotherapies that could be responsible for RP, there is limited evidence for gemcitabine (78–80), vincristine (81), 5-fluorouracil (82), oxaliplatin(83), tegafur and uracil (84) and cyclophosphamide-methotrexate-5-fluorouracil adjuvant therapy (85).

The pathophysiology of RP induced by cancer chemotherapies is not well understood, and is probably multifactorial. Some studies showed an exaggerated respond to cold not only in patients with RP, but also in patients without finger symptoms before testicular chemotherapy (62,86). An increased central sympathetic vasoconstrictor reflex and an impaired vasomuscular, non-neurogenic auto-regulation was highlighted on patient suffering

of RP syndrome after chemotherapy when compared with the control group (patients after chemotherapy without RP) (87). Currently, one of the main hypothesized mechanism is vascular damage induced by chemotherapy, which induces endothelial dysfunction that persists after chemotherapy (63). Indeed, some author (88) showed that microalbuminuria, considered to be a sign of endothelial damage, is significantly higher in patient who received testicular cancer chemotherapy (83). Another supposed mechanism is neurotoxicity of chemotherapies affecting arteriolar tone regulation. Particularly through hypomagnesia related to cisplatin administration leading to dysregulation of vascular smooth muscle tone (77). It is interesting to note that bleomycin is used to induce a sclerodermic phenotype in animals (89). Scleroderma is a major etiology of secondary Raynaud's phenomenon.

2.2. Non-medical

Vinyl chloride exposure is long time related(90) to RP. The vascular endothelium toxicity of vinyl chloride exposure has been shown by angiographic studies of hand arteries and by capillaroscopy(91,92). The prevalence of RP in vinyl chloride workers ranges from 6 to 33%(93). In 1980 a prospective exposed/non-exposed cohort study showed a strong association between vinyl chloride exposure and RP ($p < 0.006$)(94).

Table 1. Most relevant prevalence and level of evidence (defined by HAS criteria) of the association between each drug and RP

Mechanism	Drugs	Prevalence	Level of evidence
Enhancing vasoconstriction	Clonidine	Unknown	C
	Beta-blockers	7%	A
	Ergo alkaloids	0.1%	C
	Dopaminergic agonist	Unknown	C
	SSRIs	Unknown	D
	Sympathomimetic drugs	Unknown	B
Endothelial damage	Chemotherapies	20,7-37%	A
	Vinyl Chloride	6-33%	A
Drugs increasing blood viscosity and enhancing vasoconstriction	Interferons	13.6%	B
	Cyclosporine	Unknown	B
Unknown mechanism	Tyrosine Kinase Inhibitors	Unknown	D

3. Drugs increasing blood viscosity and enhancing vasoconstriction

3.1. Interferons (IFN)

RP is a known side effect of treatment of interferon supported by numerous cases reports (36,95–103). On direct questioning of patients on IFN (104), symptoms of RP are reported by more than half of them. Analysis of 24 cases reports of RP associated to interferon (105) highlighted that IFN α is the most common substance implicated (n=14), followed by IFN γ (n=5) and IFN β (n=3). The treatment period was variable and lasted from 2 weeks to 49 months (mean: 15.5 months). Clinical findings varied from mild and transient vasospasm (1 hour after injection) to digital necrosis in 14 cases. Outcomes were known for 15 patients. Spontaneous recovery was obtained for 50% of them after withdrawn of the drug. The

remaining patients needed specific medication and 6 amputations were necessary, underlying severity of this side effect. A recent meta-analysis(106) with 6 eligible studies and 183 patient estimated prevalence of RP, on patients taking interferon, of 13.6% (95% CI 0.026- 0.313).

Pathophysiology of this side effect is not currently fully understood. However numerous hypothesis have been proposed: a direct vasospastic effect (100,107), an increasing levels of intracellular endothelial cells basic fibroblast growth factor leading to proliferation of these cells and increasing angiogenesis(108), induction or exacerbation of a dormant collagen disease(96). Although some cases reports of RP induced by interferons are described without any dysimmunity trouble(109) it is known that interferon therapy can be related to autoimmune disease (110,111). Increasing blood viscosity by induction of serum cryoprecipitate(112), deposition of immune complexes(113)and arterial occlusion by thrombi due to procoagulant activity of interferon(99,100)have also been proposed. A study on 108 patients with SSc found a higher level of IFN gamma on patients with RP associated, and suggest a pathogenic role of INF-gamma in SSc patients with RP but this role still remain unclear (114).

3.2. Cyclosporine

A study assessing the prevalence of RP in 100 renal transplanted patients treated with cyclosporin monotherapy who were then converted to prednisolone and azathioprine observed development of de novo symptoms in 39% of patients with the introduction of cyclosporine, and after withdrawal of cyclosporin symptoms improved in 89% (115). Moreover four cases of RP induced by cyclosporine use have been described. Three of them emerged few days after cyclosporine introduction and totally disappeared after cessation(116,117). The second case was dose related but persisting of RP symptom was observed after cessation on cyclosporine (118). The mechanism of cyclosporine induced RP remains unclear. A

vasospastic effect of cyclosporine on both macro- and microcirculation has been shown(119). Furthermore, change of the viscosity of blood, decrease the deformability of red blood cells and increase the aggregation of platelets could also being induced by cyclosporine use and participate to RP (116).

4. Unknown mechanism

4.1. Tyrosine kinase inhibitors

The relationship between tyrosine kinase inhibitors (TKI) and RP is complex. Experimental studies have shown that receptors with a tyrosine kinase activity receptors may play a role in the exaggerated vasoconstriction in respond to cold (120). On one hand, a pilot study (121)including three SSc patient treated with 100 mg/day of imatinib for 6 months showed improvement of their RP (86). Indeed in each patient, RP was attenuated at around 3 months and had completely disappeared at 6 months. On the other hand, the exact opposite reaction has been described with other TKI. Emergence of a RP during the first week of treatment with nilotinib has been described in two patients (122). One of them experienced improvement after the treatment was switch for imatinib, and recurrence of RP with the reintroduction of nilotinib. Another patient experienced recurrent RP with nilotinib(123). Erlotinib had also been suspected in the case of a patient who experienced digital necrosis 20 days after starting a 150mg daily oral treatment (124). This 72 years old patient was suffering from scleroderma and secondary RP. Successful treatment was conducted with calcium channel blockers, nitrates, and anti-platelet drugs. This role of erlotininib was scored as a probable adverse drug reaction (7/10 on the Naranjo scale).

To our knowledge, no pathophysiologic mechanism has been identified yet.

4.2. Other

Within literature sporadic cases reports of RP potentially induced by drugs can be found. like two cases of fluorescein induced RP (125,126), sulfasalazine (127,128), propofol (129) amphotericin B(130)without being able to determine pathophysiological mechanism. Some paradoxical reactions following repeated administration of iloprost (131) or yohimbine(132), a selective α_2 adrenergic antagonist, have even been described.

Conclusion

Raynaud' phenomenon is complex, multifactorial and not fully understood yet. Microvascular impairment is a key feature of its pathophysiology, and vasodilators such as calcium channel blockers or phosphodiesterase-5 inhibitors have been proposed as a treatment for RP. On the other hand, vasoconstrictors have long been known to induce or aggravate RP. However, drugs may induce RP through a variety of other mechanisms that we have detailed in the present review. Our research also highlights the lack of available evidence regarding drug-induced RP prevalence and clinical presentation. When these treatments are started in patients with history of RP a careful attention must be given and, if possible, alternative therapies, which do not alter peripheral blood flow, should be considered.

Peripheral vasoconstriction induced by beta-blockers: a systematic review and a network meta-analysis.

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Introduction

Beta-blockers are a long known cause for drug-induced peripheral vasoconstriction (PV), especially for Raynaud's phenomenon (RP), which has been described as an adverse effect of beta-blockers forty years ago(133). Among the etiologies of the syndrome, beta-blockers usually appear as the primary cause of drug-induced RP in recent state-of-the-art reviews and textbooks (1,21,134–136).

However, little is known about the exact prevalence of beta-blocker induced peripheral vasoconstriction. Analyze of the Framingham Heart study identified beta-blockers use as the most common cause of secondary RP (34.2% of etiology of secondary RP)(137). More recently, a meta-analysis including 13 studies found a prevalence of 14.7% in patients receiving beta-blockers(138). However, included study were old (1971 to 1984) and of poor methodological quality.

The mechanism leading to peripheral vasoconstriction induced by beta-blockers is also unknown. The inhibition of β_2 -adrenoceptors, which are responsible for peripheral arteriolar vasodilatation, has long been thought to be the main mechanism. However, this hypothesis is challenged by clinical observations of RP occurring in patients taking beta-blockers with higher affinity with β_1 -adrenoceptors (133,139), and by previous pharmacology studies (14). Moreover, the presence and the involvement of β_2 -adrenoceptors in pathogenesis of RP is not currently hypothesized (9). This led to contra-indicate non selective beta-blockers in patients with RP. Another hypothesis would involve the vasoconstrictor sympathetic reflex mediated by baroreceptors in response to the decrease of cardiac output following beta-blocker intake (140). In accordance to this hypothesis, beta-blockers with intrinsic sympathomimetic activity (ISA) should induce less peripheral vasoconstriction. But limited evidence support this hypothesis, and results are conflicting (12,15,16).

The paradox is that a considerable amount of large, randomized, controlled trials have been conducted in the past decades, providing sufficient evidence to clarify the implication of beta-blockers peripheral vasoconstriction, and especially in RP. In the past few years, the development of sophisticated methods such as the combination of direct and indirect comparisons in network meta-analyses has been successfully applied to identify class adverse drug events.

Our objective in the present work was therefore to perform a systematic review and a network meta-analysis of randomized clinical trials to assess the effect of beta-blockers on peripheral vasoconstriction. We aimed at assessing the prevalence of peripheral vasoconstriction induced by beta-blockers and to compare the risk of each drug to induce such adverse effect.

Methods

This systematic review complies with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) statement guideline (141). The protocol and systematic search strategy of the review is documented online (PROSPERO registry-CRD42014014374)

1. Study identification and selection

We searched randomized controlled trials (RCTs) of beta blockers published in core clinical journals in Pubmed database. The following beta blockers were explored: Acebutolol, Atenolol, Betaxolol, Bisoprolol, Carvedilol, Celiprolol, Labetalol, Metoprolol, Nadolol, Nebivolol, Oxprenolol, Pindolol, Propranolol, Sotalol and beta-blockers. Applied filters were (Comparative Study [ptyp] OR Clinical Trial [ptyp]) AND jsubsetaim [text]. We also searched google scholar, the reference lists of relevant Cochrane reviews (142–144) and the reference list of the Trial Result-center (<http://www.trialresultscenter.org>). There were no restrictions on language or publication date. One reviewer (CK) screened titles and abstracts for inclusion. Then two reviewers (MR and CK) independently reviewed the full-text of

potentially relevant articles to determine inclusion using a standardized form according to inclusion and exclusion criteria. Eligibility criteria included parallel or crossover, randomized controlled trials (RCTs) comparing the previously listed beta blockers to a control group (placebo or any treatment) for at least 4 weeks and reporting RP or any relevant symptom linked to peripheral vasoconstriction.

Two authors (CK, MR) made independent assessments of risk of bias using the Cochrane Handbook for Systemic Reviews of Interventions (145). We rated the overall risk of bias for each trial that was defined as high-risk if more than three high-risk criteria were met, moderate-risk if two to three high-risk criteria were met, and low-risk if less than one high-risk criterion was met.

Then, the same two reviewers independently extracted data and appraised the quality and content of included studies using the Grading of Recommendation Assessment, Development and Evaluation (GRADE) recommendations for network meta-analysis (146). These recommendations permit to appraise the quality of each direct and indirect pairwise comparisons of the NMA considering the average risk of bias (147), inconsistency (148), indirectness (149), imprecision (150) and publication bias (151). Finally we rated their quality as very low, low, moderate or high. A special attention was carried on the way used to record the side effects (spontaneous reporting, medical visit, questionnaire...).

The following data were extracted: year, sample size, methodology, Raynaud phenomenon as a non-inclusion criterion, indication, follow-up period, beta-blocker characteristics (international non-proprietary name, dosage and treatment duration), definitions of outcomes (verbatim used), and frequency of outcomes (prevalence and/or withdrawals).

2. Statistical analysis

The network meta-regression was performed the R statistical software (version 3.2.0) with two complementary sets of tools: a frequentist approach, allowing to perform meta-regression, and a bayesian approach, allowing to compute rankogramm and indirect effects.

In the frequentist approach, using the metafor package, we used the arcsin transformation to compare groups. It enables comparisons with empty cells without continuity corrections and provides a narrow variance estimate(152). We also present results using the classical log odd-ratio for a simpler clinical meaning.

In the bayesian approach, using the gemtc package (with the rjags Gibbs sampler), we used the log odd-ratio transformation using a +1 continuity correction for empty cells. Indirect comparisons were computed using the node-splitting algorithm. Confidence or credibility intervals, resp., are given for all measures and represented in forest plots.

The meta-regressions were performed using metafor, yielding the regression coefficient for covariates of interest as well as the associated p-value for non-zero testing.

Results

1. Characteristics of studies and patients

The literature search yielded a total of 2238 references. The main reasons for excluding studies were that they were not randomized clinical trials, in vitro studies. Thirty eight studies fulfilled the eligibility criteria (153–190). (Figure 2)

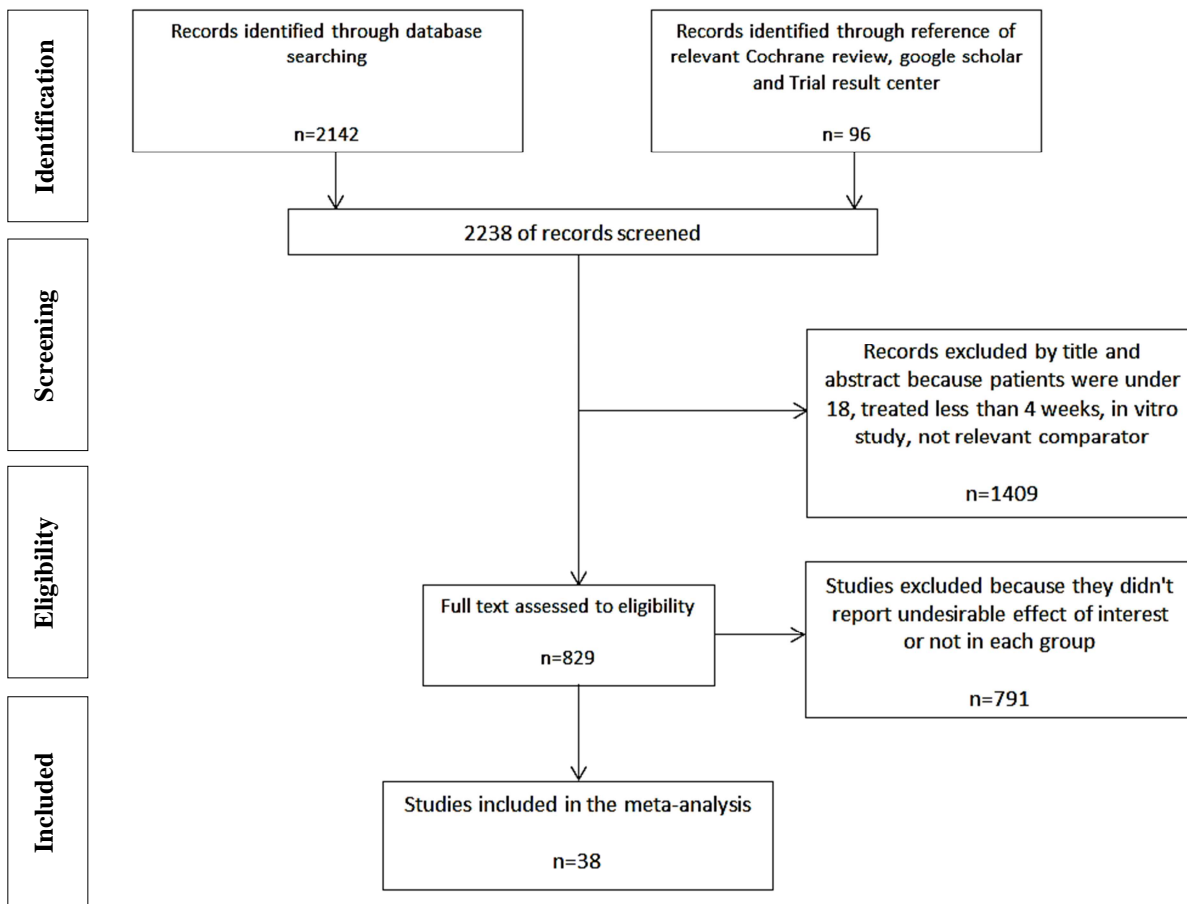


Figure 2. Flow chart

All studies were randomized controlled trials with study durations ranging from 4 to 468 weeks and including 57 026 patients. Most of the trials were multicenter and parallel, conducted in Europe or North America and examined a beta-blocker as antihypertensive treatment and included an active comparator (27/38). For more than half of them, the presence of RP was a non-inclusion criterion (20/38). Characteristics of included studies are presented in Table 2.

Table 3. Study characteristics

Study	Country	Outcome	Treatment	N	Methodology	RP exclus	Exposition (weeks)	Double blind	RP symptom (verbatim)
DiBianco 1982	USA	Angor	Acebutolol, propranolol, placebo	46	crossover	N	9	O	Cold extremities
Dahlöf 2005	UK-Scandinavian	HTA	Atenolol,DHP	19257	parallel	O	287	N	Peripheral coldness
Dahlöf2002	USA-UK-Scandinavian	HTA	Atenolol, IEC/ARA2	9193	parallel	O	209	O	Cold extremities
Talseth 1991	Norway	HTA	Atenolol, alpha blocker	164	parallel	N	157	O	Peripheral ischemia
NASRC 1988	UK	HTA	Atenolol, DHP	410	parallel	O	12	O	Peripheral ischemia or pain
Ott 1987	Denmark	HTA	Atenolol, alpha blocker	126	parallel	N	20	O	Cold extremities
Fairhurst 1986	International	HTA	Atenolol, bevantolol, placebo	229	parallel	N	12	O	Peripheral vascular side effect
Helgeland 1986	Norway	HTA	Atenolol, IEC/ARA2, thiazidique	400	parallel	O	14	O	Cold extremities
Rubin 1983	UK	HTA	Atenolol, placebo	85	parallel	O	36	O	Raynaud's Phenomenon
Julian 1982	UK	IDM	Sotalol, placebo	1456	parallel	N	26	O	Cold extremities
Hansteen 1982	Norway	IDM	Propranolol, placebo	560	parallel	O	52	O	Cold hand and feet
Persson 1995	Sweden	IDM	Metoprolol, xamoterol	121	parallel	N	52	O	Cold extremities
Greenberg 1984	UK	HTA	Propranolol, thiazidique, placebo	7241	parallel	N	256	N	Raynaud's Phenomenon
BHATRG 1982	USA	IDM	Propranolol, placebo	3837	parallel	O	109	O	Cold hand, feet
Silberstein 2012	Norway	Migraine	Propranolol, placebo	191	parallel	O	261	O	Peripheral coldness
Leren 1980	France	Angor	Propranolol, alpha blocker	23	crossover	N	8	O	cold hand and feet
Pascal 1987	USA	VB	Propranolol, placebo	230	parallel	O	62	N	Raynaud Phenomenon
Moltzer 2010	Italy	HTA	Metoprolol, IEC/ARA2	16	crossover	O	16	N	Cold extremities
Metra 2001	Scotland	IC	Metoprolol, carvedilol	150	parallel	O	100	O	Raynaud phenomenon
Herrick 1989	UK	HTA	Atenolol, IEC/ARA2	162	parallel	O	12	O	Cold extremities
Taylor SH 1982	UK	IC	Oxprenolol, placebo	1103	parallel	N	209	O	Cold extremities
UKPDS 1998	Germany	DT2	Atenolol, IEC/ARA2	758	parallel	N	438	O	Cold hand and feet
The DTS Group 1993	Europe	IDM	Atenolol,placebo	1473	parallel	O	157	O	Cold extremities
The IPPPSH Group 1985	Sweden	HTA	Oxprenolol, placebo	6357	parallel	N	209	O	Cold extremities
Ekbom T 1992	Sweden	HTA	Metoprolol, atenolol, pindolol, placebo	1021	parallel	N	52	O	Cold hand and feet
Garden OJ 1990	UK	VB	Propranolol, placebo	81	parallel	N	104	O	Cold extremities
Nielsen 1997	Denmark	HTA	Atenolol, IEC/ARA2	36	parallel	N	183	N	Cold extremities
Beevers 1991	UK	HTA	Atenolol, IEC/ARA2, placebo	288	parallel	O	8	O	Cold extremities
Khattar 2001	UK	IC	Carvedilol, IEC/ARA2	57	parallel	N	12	O	Cold peripheries
Mc Neil 1979	Australia	HTA	Metoprolol, pindolol, atenolol, labetalol	29	crossover	N	10	O	Cold extremities
Pasotti 1982	Italy	HTA	Pindolol, metoprolol	16	crossover	O	12	O	Cold extremities
Iliuta 2009	Romania	CABPG	Betaxolol, metoprolol	1352	parallel	N	4	O	Cold extremities
Vandenburg 1984	UK	HTA	Propranolol, alpha blocker	60	parallel	O	10	N	Cold extremities
Detry 1994	International	Angor	Propranolol, Trimetazidine	149	parallel	O	12	O	Cold extremities
Salonen 1992	Finland	HTA	Betaxolol, placebo	60	crossover	N	4	O	Cold hand and feet
Bühler 1986	Europe	HTA	Bisoprolol, atenolol	94	crossover	O	8	O	Cold extremities
De Muinck 1992	Europe Nord	Angor	Bisoprolol, atenolol	175	parallel	N	12	O	Cold extremities
Pedersen 1976	Denmark	HTA	Metoprolol, Thiazidique	20	crossover	N	8	O	Cold extremities

Studies included were crossover studies in 7 cases. Out of a total of 38 trials, 32 were double blind while 6 were single blind. The risk of bias of included studies was appraised considering allocation concealment, blinding, accounting of patients and outcome events, selective outcome reporting or carryover effects in

crossover trial.(145,147) This risk of bias was widely irregular between studies, 8 studies were considered as high risk of bias whereas methodology was considered as high quality for 8 included studies too (Figure 3).

	Random sequence generation	Allocation concealment	Blinding participant/personnel	Blinding outcome assessment	Incomplete outcome data	Selective reporting	Other biases
DiBianco 1982	+	+	+	-	-	+	
Dahlöf 2005	+	+	-	+	+	+	
Dahlöf 2002	+	+	+	+	+	+	
Talseth 1991	+	+	+	-	-	+	
NASRC 1988	+	+	+	+	-	+	
Ott 1987	?	?	+	-	-	+	
Fairhurst 1987	?	?	+	?	-	+	
Helgeland 1986	?	?	+	-	-	+	
Rubin 1983	?	?	+	+	-	+	
Julian 1982	+	+	+	-	+	+	
Hansteen 1982	+	+	+	-	+	-	
Persson 1995	?	?	+	-	+	+	
Greenberg 1984	?	?	-	?	+	+	
BHATRG 1982	?	?	+	-	-	+	
Silberstein 2012	+	+	+	+	+	+	
Leren 1980	?	?	+	-	-	-	
Pascal 1987	+	+	-	+	+	+	
Moltzer 2010	?	?	-	-	+	+	
Metra 2000	?	?	+	-	+	+	
Herrick 1989	+	+	+	-	+	+	
Taylor SH 1982	+	+	+	+	+	+	
UKPDS 39 1998	+	+	+	-	+	+	
The DTS Group 1993	+	+	+	+	+	+	
The IPPPSH Group 1985	+	+	+	+	+	+	
Ekblom T 1992	?	?	+	+	+	+	
Garden OJ 1990	?	?	+	-	+	+	
Nielsen 1997	?	?	-	?	+	+	
Beevers 1991	?	?	+	-	+	+	
Khattar 2001	?	?	+	-	+	+	
Mc Neil 1979	?	?	+	-	+	+	
Pasotti 1982	?	?	+	-	+	+	
Iliuta 2009	?	?	+	-	+	+	
Vanderburg 1984	?	?	-	-	+	+	
Detry 1994	?	?	+	+	+	+	
Salonen 1992	?	?	+	-	+	+	
Bühler 1986	?	?	+	-	+	+	
De Muinck 1992	?	?	+	-	+	+	
Pedersen 1976	+	?	+	-	+	+	

Figure 3. The risk of bias summary.

+ = Low risk of bias; - = high risk of bias; ? = unclear risk of bias

2. Network and methodological quality of available comparisons

34 direct comparisons between beta-blockers and controls were available. Controls mostly include placebo, ACE/ARB, α blockers and thiazide diuretic. Network of available comparisons is represented in Figure 4.

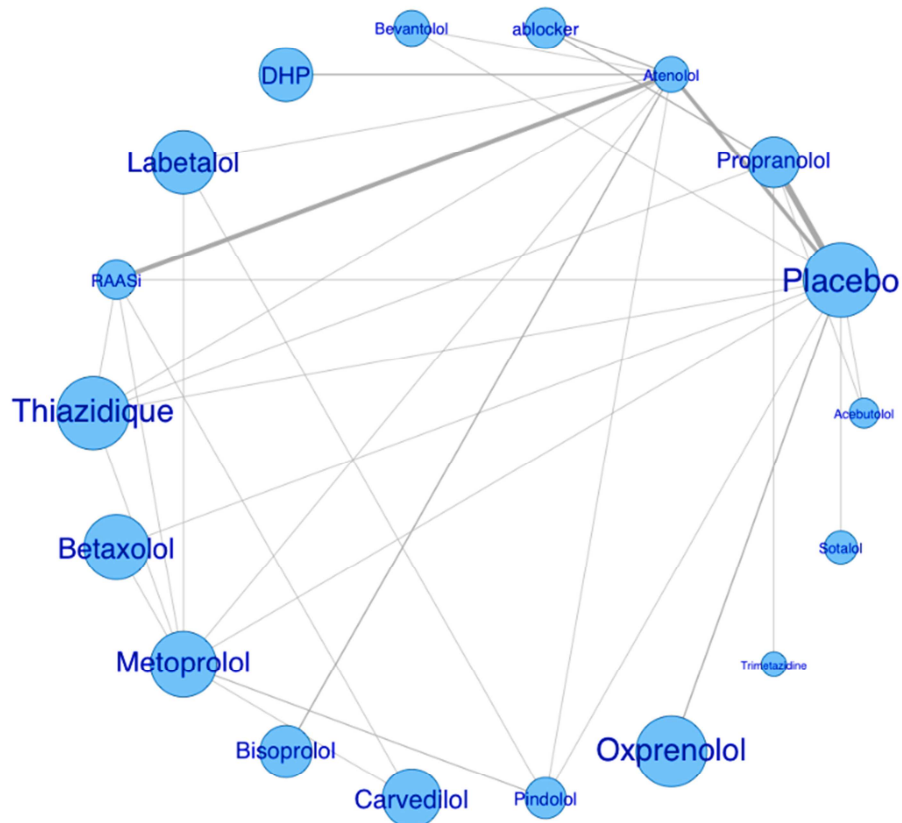


Figure 4. Network of available comparisons between the different beta-blockers and controls. Size of node is proportional to number of trials participants and thickness of the lines is proportional to number of trials that included the direct comparisons.

We used and followed GRADE recommendation to appraise and rate the quality of evidence of our network meta-analysis. This approach allows estimating the risk of bias of each direct and indirect comparison across the NMA. The results are presented in Supplementary Table S1.

3. Peripheral vasoconstriction induced by beta-blockers

The prevalence of PV among patients treated with beta-blockers was 7% (1966/28072), whereas 4.6% (555/12060) and 1.7% (305/17492) of patients treated with placebo or active control experienced PV, respectively ($P < 0.001$).

Network meta-analysis of direct and indirect comparisons between the different beta-blockers revealed differences between drugs (Figure 3; supplementary Figure S2). Propranolol (OR=3.0 [1.4-6.6], high quality evidence), atenolol (OR=2.0 [0.9-4.7], moderate quality evidence) and metoprolol (OR=1.7 [0.47-4.8], high quality evidence) were significantly associated with an increase of RP or cold extremities (atenolol and metoprolol were significantly associated with PV in the Arcsin model but not in the Bayesian model which resulted the OR and the credible intervals).

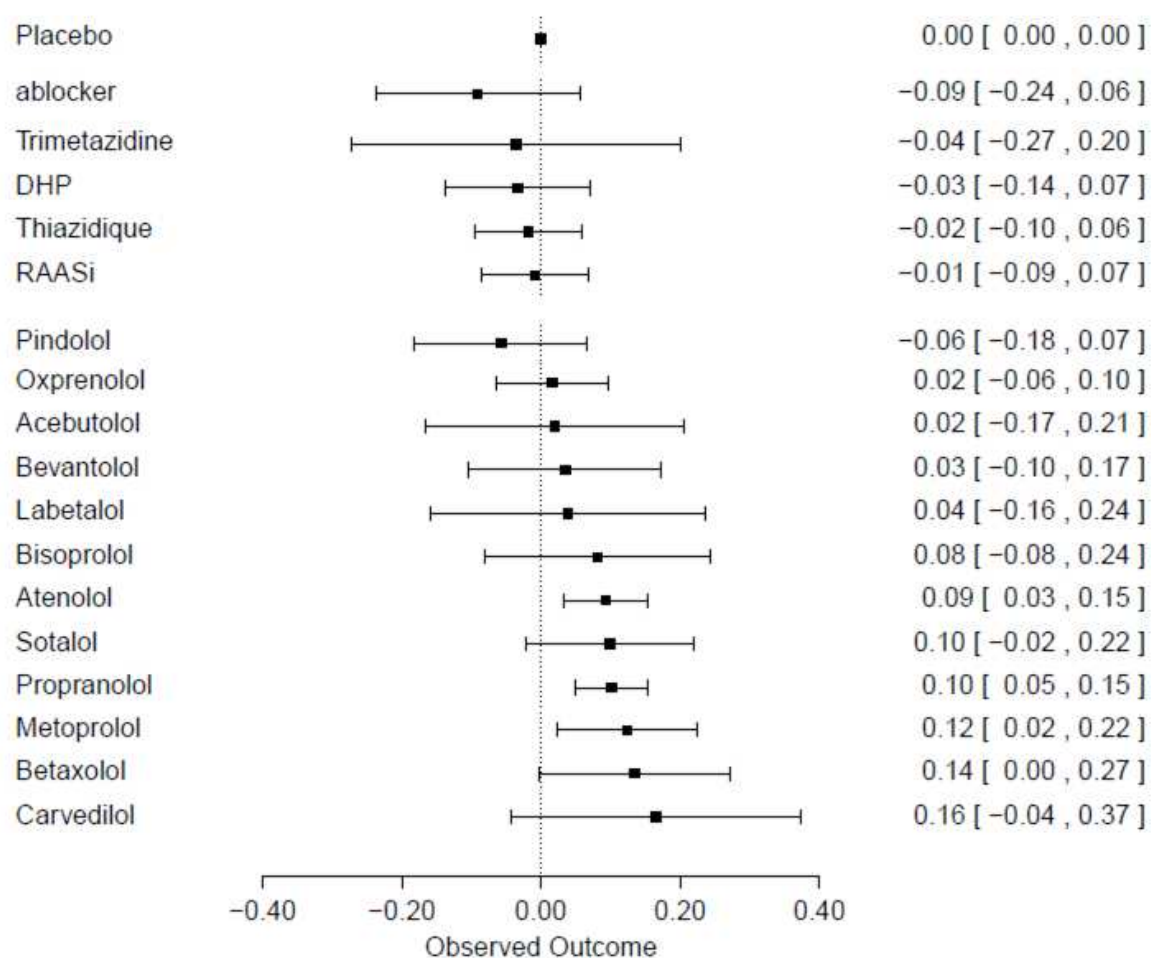


Figure 5. Forest plot, effect size estimated through the arcsin difference.

4. Influence of pharmacologic properties of beta blockers on PV

Into assess the influence of the different pharmacologic properties of beta blockers on the risk of PV we categorized beta-blockers in 4 groups (ISA, β_1 selectivity, vasodilators, and non-selectives), depending of their secondary properties (presented in Table 3). Prevalence of PV in each group was 1.1 % [0.5-1.8], 3.9 % [3.3-4.4], 6.4 % [6.1-6.8], 11.5 % [10.6-12.4] respectively.

Then we performed a meta-analysis of these 4 groups versus placebo, in a random effect model. Results in Figure 5. Only beta-blockers owning a β_1 selectivity and the non-selectives beta-blockers were linked to an increase of PV compared to placebo (Figure6).

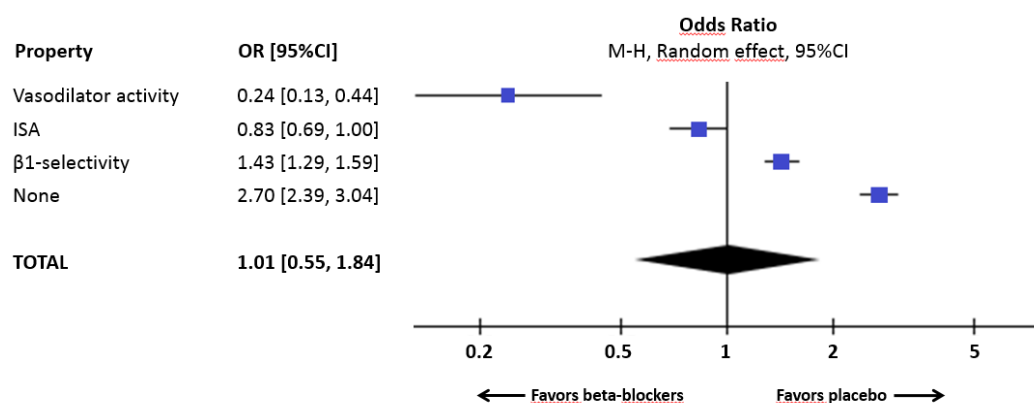


Figure 6. Results of sub-group analysis versus placebo using a random effect model.

5. Sensitivity analyses: way to report RP, latitude, dosage, indication, year of publication.

Prevalence of PV widely fluctuates according to the way to report unwanted effect: 13, 47% with a questionnaire and 6.02% with spontaneous report in the population taking beta-blockers. In the placebo group it is 8.1% with a questionnaire and 4.84% on spontaneous report.

We also performed a meta-regression model considering sequentially study latitude, drug indication, drug doses and year of publication. For each of these covariates, we show the p-value of the significance of this covariate in the meta-regression model.

- *Latitude* ($P=0.18$)
- *Dosage: low* ($P=0.67$), *normal* ($P=0.86$), *high* ($P=0.82$).
- *Indication: variceal bleeding* ($P=0.71$), *hypertension* ($P=0.24$), *ischemia* ($P=0.27$)
- *Year of publication* ($P=0.19$)

All these sensitivity analysis were not conclusive.

Discussion

In our study 7% of the 28072 patients taking beta-blockers suffered from RP or cold extremities, whereas they were only 4.6% under placebo. We show that beta-blockers represent a highly heterogeneous family regarding their propensity to induce RP, and those ancillary properties such as vasodilator effect or ISA are protective.

The present work brings additional information about the prevalence of peripheral vasoconstriction induced by beta-blockers. The prevalence of 7% of PV found in our study is lower than in the studies assessing it in the general population. A general practice based study in the UK found that 14.5% of patients responding to a postal survey and 19% of patients attending surgeries have RP related symptoms. (5). A community based study from the US reported RP in 11% of women and 8% of men (6). The prevalence of 14.7% of RP in patients receiving beta-blockers found in the 2012 meta-analysis was also close higher (138). Included studies were clinical-, cohort-, or case-control studies and for most of them RP symptoms were also reported using a questionnaire. First, in most of included studies in the NMA RP

was an exclusion criteria (20/38). Secondly, these assessments were realized using questionnaire describing symptoms of RP and these results are close to those found among included studies reporting side effects with a questionnaire (13.5%) (161,162,176,177,179,182,188). Thirdly, there was an important heterogeneity between studies, the most striking example being atenolol, for which the prevalence of PV ranged from 0 to 84% (172,179). This wide variability translates differences in the definition of RP or cold extremities and, in most cases, to the lack of objective criteria to assess peripheral vasoconstriction. Moreover the variability of geographic locations is known to influence the prevalence of RP (191) although it was not significant in our study.

All beta-blockers share a common feature relative to their action at β_1 -adrenoceptors producing the cardiovascular effects. However, they differ in their affinity for the subtypes of β -adrenoceptors, as well as in their actions on other receptors and subsequent ancillary properties. For example, propranolol and other non-selective beta-blockers also exert an antagonist effect on β_2 -adrenoceptors, which has long been thought to be the cause of PV induced by beta-blockers. However, our study shows that drugs with higher affinity for β_1 than for β_2 -adrenoceptors, such as metoprolol and atenolol, also induce significantly more RP than placebo.

Beta-blocker	β 1-selectivity	ISA*	MSA**	Vasodilator activity	Half life (hours)	Mean usual hypertension dose (mg/d)	Clinical application	USA	CI in France
• Propranolol	0	0	++	0	3.5-6	160	Hypertension, angina	No	Yes
• Nadolol	0	0	0	0	14-24	160	pectoris, migraine,	No	Yes
• Sotalol	0	0	0	0	12	160-320	hyperthyroidism, arrhythmias	No	Yes
• Metoprolol	+	0	0	0	3-4	100-200	Hypertension, angina	Severe form	Severe form
• Atenolol	+	0	0	0	6-9	50-100	pectoris, arrhythmias	Precaution	Severe form
• Betaxolol	+	0	0	Ca ⁺⁺ entry blockade	14-22	20		No	Severe form
• Nebivolol	+	0	0	Nitricoxide release	11-30	5-10		Precaution	Severe form
• Bisoprolol	+	0	0	0	9-12	5-10		Precaution	Severe form
• Bevantolol	+	0	+	α ₁ receptor blockade Ca ⁺⁺ entry blockade	2	150-300		No AMM	No AMM
• Xamoterol	+	+	0	0				No AMM	No AMM
• Pindolol	0	++	0	0	3-4	15	Hypertension, migraine, arrhythmias	No	Yes
• Acebutolol	+	+	+	0	3-4	400		Precaution	Severe form
• Oxprenolol	0	+	+	0	1-2	320		No AMM	Yes
• Celiprolol	+	+	-	β ₂ receptoragonist Nitricoxide release	4-5	200-400		No AMM	No
• Carvedilol	0	0	0	α ₁ receptor blockade Ca ⁺⁺ entry blockade Antioxidant activity	7-10	25-50	Heart failure	Precaution	Yes
• Labetalol	0	0	0	α ₁ receptor blockade	5	400	HTA	No	No

Table 4. Beta-blockers characteristics. We excluded betablockers used only for ophthalmic use in France: Alprenolol, carteolol, levobunolol, metipranolol, penbutolol and timolol. 0 = absent or low; + = moderate; ++ = high; - = no information; * ISA=Intrinsec sympathomimetic activity;** MSA = Membrane-stabilising activity

Cold hand and RP were promptly linked to the use of the first beta-blocker, propranolol (192). Propranolol is a non-selective β_1 and β_2 antagonist devoid of ISA and vasodilator activity. Influence of β_2 -adrenoceptors was first incriminated in the pathophysiology of cold hand related to beta-blocker intake. Indeed β_2 -adrenoceptors are the source of a vasodilator tone of blood vessel in skeletal muscle. However, no study showed a difference in the frequency of the feeling of cold hand and the β_1 -selectivity property of beta-blockers (17,193,194). Later a link between ISA and the reduction of the feeling of cold hand was hypothesized. Beta-blockers devoid of ISA induced when started a reflex vasoconstriction mediated by the baroreceptors and proportional to the reduction of the cardiac output. The lack of difference between beta blockers with or without β_1 -selectivity supposes that this reflex is mediated by vasoconstrictors α_1 and α_2 adrenoceptors. Beta-blockers owning ISA induced less fall in cardiac output and did not produce this reflex of vasoconstriction (140,195). Pindolol is the most important beta-blocker with this property followed by acebutolol, celiprolol and oxprenolol. These beta-blockers are those who induced least cold extremities symptoms in our study. Not only this reflex of vasoconstriction is absent but studies even observed a decrease of peripheral vascular resistance on patients taking beta blockers with a strong ISA (140,195). A study explored the local hemodynamic effect of pindolol in healthy volunteers and the change in the forearm blood flow (FBF) in response to infusion of beta-blockers in the brachial artery. They observed a dose dependent increase of the FBF following pindolol infusion without inducing changes in heart rate or blood pressure. This increase of FBF induced by pindolol was reduced by concomitant infusion of propranolol but not totally, suggesting an additional local effect on vascular smooth muscle tone (196). These studies were followed by *in vitro* experimentations who showed that the ISA of pindolol is so important that stimulation of β_2 adrenoceptors is produced, leading to vasodilatation. Here as

well, the relaxation produced by pindolol or celiprolol could be antagonized but not abolished by pretreatment with propranolol or sotalol.(197–199) However no evidence of involvement of α_1 and α_2 subtypes receptors to pindolol vasodilator activity was highlighted and they also suggested an additional local effect on vascular smooth muscle tone. In our study bevantolol and labetalol two beta blockers owning a vasodilator activity through α_2 antagonism belongs to the beta blockers who induce least PV. Observation in line with the implication of these receptors in the pathophysiology of beta blocker PV .It should be noted that involvement of this α_2 adrenoceptor function is one of the main etiologic mechanisms of non-iatrogenic RP.(1)

The clinical relevance of ISA was highlighted for example in a double blind double dummy randomized crossover study (n=39) comparing pindolol to propranolol the symptoms severity of cold extremities was significantly reduced during pindolol period compared with placebo period and increased during propranolol period. (18) A UK study including 7659 patients with hypertension in general practice found that the feeling of cold extremities is more pronounced in patients taking beta-blockers than other hypertensive treatment (4.1% vs 0.2%), notably those taking beta-blockers with ISA complained less frequently than those on beta blockers without (3.1% vs 5.2%)(17).

Surprisingly, all studies exploring the effect of beta blockers on patients with a primary RP failed to show worsening of their symptoms. Indeed, a 1994 review of peripheral vascular effect of beta-blocker(140) conclude that there is no evidence of any adverse effects of beta-blocker treatment on peripheral circulation without pre-existing peripheral vascular disease. Furthermore, in accordance to this model beta-blockers with intrinsic sympathomimetic activity should theoretically provide less RP. But available data didn't found any difference in the prevalence of cold extremities among patients on alprenolol, atenolol, metoprolol, pindolol and propranolol.(16) Furthermore, no difference in onset of RP in controlled clinical

trials was shown between beta-blockers and placebo. In a crossover, randomized, double-blind clinical trial, on normotensive patients suffering from primary Raynaud phenomenon (n=16), crisis frequency and digital blood flow between metoprolol, propranolol or placebo were comparable(12). Another double-blind, randomized, placebo-controlled study patients with a primary RP, had investigated the effects of propranolol, metoprolol, and pindolol on finger skin temperature and blood flow. They didn't found any difference between nonselective beta-blocker propranolol, the β_1 -selective beta-blocker metoprolol, the nonselective beta-blocker ISA pindolol and of placebo.(14) Another crossover, double blind, trial on hypertensive patients with primary RP did not found worsening of symptoms between placebo and propranolol or labetalol period (15). But we know that pathophysiology of RP is complex, mediated through a wide variety of mechanisms, and vasospastic attacks were observed even after nerve block (200).

The results of this work challenge the relevance of the contraindication of beta-blockers in primary RP. In France, carvedilol, nadolol, oxprenolol, pindolol, propranolol and sotalol are contraindicated with RP; acebutolol, betaxolol, bisoprolol, metoprolol, nebivolol only in severe forms; whereas celiprolol and labetalol are not contraindicated.

Network meta-analysis is a relevant approach in pharmacovigilance, especially to test the homogeneity of a class adverse effect. Although this methodological approach is becoming more accessible thanks to the availability of dedicated statistic packages, it is still under used in safety studies. In parallel, the development of approaches and recommendations to appraise the quality of a treatment effect estimated from a NMA participate to standardize practices. To our knowledge this is the first NMA with a safety purpose following the GRADE recommendation to assess the quality of direct and indirect comparisons. This approach includes assessment of 5 items for each pairwise comparison (risk of bias(147), inconsistency(148), indirectness(149) and imprecision(150) and publication bias(151)) to

raise quality of evidence and had to be adapted to our safety studies. In our study each pairwise comparison risk of bias was assessed in the light of the weight of each study involved, as advised in GRADE recommendations. Globally, the risk of bias was relatively low in study included and fortunately the best methodological studies were the larger trials. Heterogeneity was >40% in only 2/35 pairwise comparison reflecting coherence of our results. However, the GRADE result table do not seems us readable and this homogenous presentation include in fact aggregation results of as studies as pairwise comparison present the NMA.

Limits

The findings from our analysis should be considered in light of its limitations. We reduce our literature searches in Pubmed database and core clinical journal leading possibly to a publication bias. However this study did not aimed to assess an efficacy criterion of beta-blockers, and we suppose that no clinical trial was unpublished or stopped because of RP or cold extremities.

We were unable to consider all beta-blocker drugs in our analysis: large scale randomized controlled trials are lacking for most of the older drugs and even for some newer ones.

Conclusion

Peripheral vasoconstriction induced by beta-blockers is a long time known side effect, and this network meta-analysis provides further evidence that it should not be considered as a homogeneous class effect. Ancillary properties such ISA and vasodilator effect are protective. On the other hand, higher affinity for β_1 -adrenoceptors does not protect from RP, which challenges current recommendations and contra-indications.

SUPPLEMENTARY INFORMATION

Table S1. Quality ratings following GRADE recommendations for comparison of peripheral vasoconstriction induced by beta-blockers.

Comparison	Direct evidence	Indirect evidence	Network meta-analysis
	Quality of evidence	Quality of evidence	Quality of evidence
Acebutolol v Alpha blocker		Very low	Very low
Acebutolol v Atenolol		Low	Low
Acebutolol v Betaxolol		Low	Low
Acebutolol v Bevantolol		Very low	Very low
Acebutolol v Bisoprolol		Very low	Very low
Acebutolol v Carvedilol		Very low	Very low
Acebutolol v CCB		Very low	Very low
Acebutolol v ACE/ARB		Very low	Very low
Acebutolol v Labetalol		Very low	Very low
Acebutolol v Metoprolol		Low	Low
Acebutolol v Metoprolol		Low	Low
Acebutolol v Pindolol		Low	Low
Acebutolol v Placebo	Low‡	High	High
Acebutolol v Propranolol	Moderate†	High	High
Acebutolol v Sotalol		Low	Low
Acebutolol v Thiazidique		Low	Low
Acebutolol v Trimetazidine		Very low	Very low
Acebutolol v Xamoterol		Very low	Very low
Alpha blocker v Atenolol	Moderate*	Moderate	Moderate
Alpha blocker v Betaxolol		Very low	Very low
Alpha blocker v Bevantolol		Very low	Very low
Alpha blocker v Bisoprolol		Moderate	Moderate
Alpha blocker v Carvedilol		Very low	Very low
Alpha blocker v CCB		Moderate	Moderate
Alpha blocker v ACE/ARB		Moderate	Moderate
Alpha blocker v Labetalol		Moderate	Moderate
Alpha blocker v Metoprolol		Moderate	Moderate
Alpha blocker v Oxprenolol		Very low	Very low
Alpha blocker v Pindolol		Moderate	Moderate
Alpha blocker v Placebo		Moderate	Moderate
Alpha blocker v Propranolol	Very low**, ‡	Low	Low
Alpha blocker v Sotalol		Very low	Very low
Alpha blocker v TD		Low	Low
Alpha blocker v Trimetazidine		Very low	Very low
Alpha blocker v Xamoterol		Very low	Very low
Atenolol v Betaxolol		Low	Low
Atenolol v Bevantolol	Very low**, ‡	Low	Low
Atenolol v Bisoprolol	High	High	High
Atenolol v Carvedilol		Low	Low
Atenolol v CCB	High	High	High
Atenolol v ACE/ARB	Moderate*	Moderate	Moderate
Atenolol v Labetalol	Moderate†	High	High
Atenolol v Metoprolol	Moderate†	High	High
Atenolol v Oxprenolol		Low	Low
Atenolol v Pindolol	High	High	High
Atenolol v Placebo	Moderate*	Moderate	Moderate

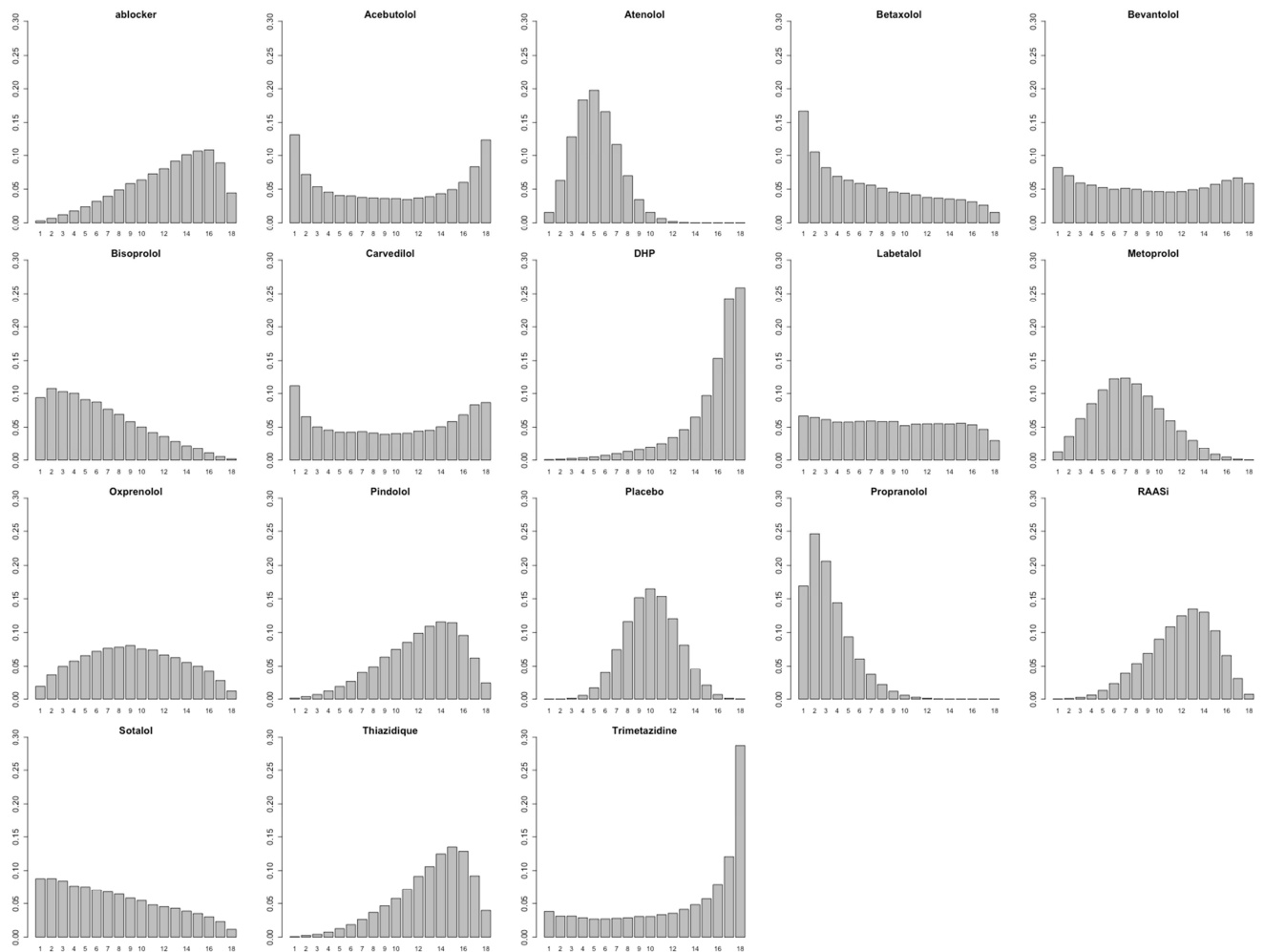
Atenolol v Propranolol		Low	Low
Atenolol v Sotalol		Moderate	Moderate
Atenolol v Thiazidique	Low**	Low	Low
Atenolol v Trimetazidine		Very low	Very low
Atenolol v Xamoterol		Moderate	Moderate
Betaxolol v Bevantolol		Very low	Very low
Betaxolol v Bisoprolol		Very low	Very low
Betaxolol v Carvedilol		Low	Low
Betaxolol v CCB		Very low	Very low
Betaxolol v ACE/ARB		Very low	Very low
Betaxolol v Labetalol		Moderate	Moderate
Betaxolol v Metoprolol	Moderate*	High	High
Betaxolol v Oxprenolol		Low	Low
Betaxolol v Pindolol		Low	Low
Betaxolol v Placebo	Low‡	High	High
Betaxolol v Propranolol		Low	Low
Betaxolol v Sotalol		Low	Low
Betaxolol v Thiazidique		Low	Low
Betaxolol v Trimetazidine		Very low	Very low
Betaxolol v Xamoterol		Moderate	Moderate
Bevantolol v Bisoprolol		Very low	Very low
Bevantolol v Carvedilol		Very low	Very low
Bevantolol v CCB		Very low	Very low
Bevantolol v ACE/ARB		Very low	Very low
Bevantolol v Labetalol		Very low	Very low
Bevantolol v Metoprolol		Very low	Very low
Bevantolol v Oxprenolol		Very low	Very low
Bevantolol v Pindolol		Very low	Very low
Bevantolol v Placebo	Very low**, †	Low	Low
Bevantolol v Propranolol		Very low	Very low
Bevantolol v Sotalol		Very low	Very low
Bevantolol v Thiazidique		Very low	Very low
Bevantolol v Trimetazidine		Very low	Very low
Bevantolol v Xamoterol		Very low	Very low
Bisoprolol v Carvedilol		Very low	Very low
Bisoprolol v CCB		High	High
Bisoprolol v ACE/ARB		Moderate	Moderate
Bisoprolol v Labetalol		Moderate	Moderate
Bisoprolol v Metoprolol		Moderate	Moderate
Bisoprolol v Oxprenolol		Very low	Very low
Bisoprolol v Pindolol		Moderate	Moderate
Bisoprolol v Placebo		Moderate	Moderate
Bisoprolol v Propranolol		Very low	Very low
Bisoprolol v Sotalol		Very low	Very low
Bisoprolol v Thiazidique		Low	Low
Bisoprolol v Trimetazidine		Very low	Very low
Bisoprolol v Xamoterol		Very low	Very low
Carvedilol v CCB		Very low	Very low
Carvedilol v ACE/ARB	Low*, †	Moderate	Moderate
Carvedilol v Labetalol		Low	Low
Carvedilol v Metoprolol	Low*, †	Moderate	Moderate
Carvedilol v Oxprenolol		Very low	Very low
Carvedilol v Pindolol		Low	Low
Carvedilol v Placebo		Low	Low
Carvedilol v Propranolol		Very low	Very low
Carvedilol v Sotalol		Very low	Very low
Carvedilol v Thiazidique		Low	Low
Carvedilol v Trimetazidine		Very low	Very low
Carvedilol v Xamoterol		Low	Low
CCB v ACE/ARB		Moderate	Moderate

CCB v Labetalol		Moderate	Moderate
CCB v Metoprolol		Moderate	Moderate
CCB v Oxprenolol		Very low	Very low
CCB v Pindolol		Moderate	Moderate
CCB v Placebo		Moderate	Moderate
CCB v Propranolol		Very low	Very low
CCB v Sotalol		Very low	Very low
CCB v Thiazidique		Low	Low
CCB v Trimetazidine		Very low	Very low
CCB v Xamoterol		Very low	Very low
ACE/ARB v Labetalol		Moderate	Moderate
ACE/ARB v Metoprolol	Very low**, ‡	Low	Low
ACE/ARB v Oxprenolol		Very low	Very low
ACE/ARB v Pindolol		Moderate	Moderate
ACE/ARB v Placebo	Very low*, ‡	Moderate	Moderate
ACE/ARB v Propranolol		Very low	Very low
ACE/ARB v Sotalol		Very low	Very low
ACE/ARB v Thiazidique	Very low**, †	Low	Low
ACE/ARB v Trimetazidine		Very low	Very low
ACE/ARB v Xamoterol		Very low	Very low
Labetalol v Metoprolol	Moderate†	High	High
Labetalol v Oxprenolol		Very low	Very low
Labetalol v Pindolol	Moderate†	High	High
Labetalol v Placebo		Moderate	Moderate
Labetalol v Propranolol		Very low	Very low
Labetalol v Sotalol		Very low	Very low
Labetalol v Thiazidique		Low	Low
Labetalol v Trimetazidine		Very low	Very low
Labetalol v Xamoterol		Moderate	Moderate
Metoprolol v Oxprenolol		Low	Low
Metoprolol v Pindolol	Low*, †	Moderate	Moderate
Metoprolol v Placebo	High	High	High
Metoprolol v Propranolol		Low	Low
Metoprolol v Sotalol		High	High
Metoprolol v Thiazidique	Low‡	High	High
Metoprolol v Trimetazidine		Very low	Very low
Metoprolol v Xamoterol	High	High	High
Oxprenolol v Pindolol		Low	Low
Oxprenolol v Placebo	Low†, §	High	High
Oxprenolol v Propranolol		Low	Low
Oxprenolol v Sotalol		Low	Low
Oxprenolol v Thiazidique		Low	Low
Oxprenolol v Trimetazidine		Very low	Very low
Oxprenolol v Xamoterol		Very low	Very low
Pindolol v Placebo	High	High	High
Pindolol v Propranolol		Low	Low
Pindolol v Sotalol		High	High
Pindolol v Thiazidique		Low	Low
Pindolol v Trimetazidine		Very low	Very low
Pindolol v Xamoterol		Low	Low
Placebo v Propranolol	Low†, §	High	High
Placebo v Sotalol	High	High	High
Placebo v Thiazidique	Low*, †	Moderate	Moderate
Placebo v Trimetazidine		Low	Low
Placebo v Xamoterol		Moderate	Moderate
Propranolol v Sotalol		Low	Low
Propranolol v Thiazidique	Very low*, ‡	Low§	Low
Propranolol v Trimetazidine	Low‡	High	High
Propranolol v Xamoterol		Very low	Very low
Sotalol v Thiazidique		Low	Low

Sotalol	Trimetazidine	Very low	Very low
Sotalol	Xamoterol	Very low	Very low
Thiazidique	Trimetazidine	Very low	Very low
Thiazidique	Xamoterol	Low	Low
Thiazidique	Xamoterol	Very low	Very low
Trimetazidine	Alpha blocker	Very low	Very low

*Risk of bias. ** Severe risk of bias. § Inconsistency. † Imprecision. ‡ Severe Imprecision

Figure S1. Rankogram



DISCUSSION ET CONCLUSION GENERALE

Ce travail consiste donc en deux études distinctes. La première, une revue systématique de la littérature nous a permis d'identifier de nombreuses classes médicamenteuses possiblement à l'origine de la survenue ou de l'exacerbation d'un RP. La physiopathologie de cet effet indésirable reste mal connue, elle est complexe et implique différents mécanismes selon les classes médicamenteuses. L'approche mécanistique utilisée dans cette revue nous a permis tout de même de faire émerger de grandes voies physiopathologiques:

- l'augmentation de la vasoconstriction périphérique via les récepteurs α_2 adrénergiques, par activation (clonidine, alcaloïdes de l'ergot, bromocriptine ; inhibiteurs de la recapture de la sérotonine ; agonistes dopaminergiques ; sympathomimétiques ; ciclosporine ; interférons) ou par neurotoxicité (chimiothérapies, chlorure de vinyle);

- l'induction de dommages endothéliaux (chimiothérapies, bromocriptine);

- la baisse du flux sanguin capillaire par l'induction de pathologies auto-immunes (interférons), par l'augmentation de l'agrégabilité plaquettaire (interférons, ciclosporine) ou par la baisse de la déformabilité érythrocytaire (ciclosporine);

- l'inhibition de l'angiogénèse a également été supposée (inhibiteurs des tyrosines kinases).

Bien que l'induction de RP soit pour certains médicaments largement connue, très peu de données fiables sont disponibles concernant leur prévalence, leur présentation clinique et leur prise en charge. Les cas rapportés sont nombreux, parfois contradictoires et, à l'exception des chimiothérapies pour lesquelles il existe des études de bonne qualité avec une relation dose-effet mise en évidence, aucune classe médicamenteuse ne peut être considérée comme pourvoyeuse de RP avec certitude. Par ailleurs le RP peut être secondaire à de

nombreuses pathologies, cela peut conduire à des erreurs d'interprétations et des biais protopathiques (hépatite auto-immune et interférons, néoplasie et chimiothérapie, migraine et dérivés ergotés...). Beaucoup de travail reste donc encore à accomplir dans ce domaine via des études contrôlées randomisées et de larges études de pharmaco-épidémiologie et de pharmacovigilance. Ces traitements doivent malgré tout être utilisés avec prudence chez les patients atteints de RP et un traitement alternatif préféré si possible.

Afin de tenter d'apporter quelques éléments de réponse à ces nombreuses zones d'ombres nous nous sommes donc ensuite intéressés plus spécifiquement à la classe médicamenteuse des bêta-bloquants. Ceux-ci sont connus pour induire des PR depuis leur mise sur le marché dans les années 1970. Ce n'est pas pour autant que cet effet indésirable est bien connu. Tous les bêta-bloquants partagent un antagonisme pour les récepteurs β_1 adrénergiques mais ils possèdent par ailleurs de nombreuses autres propriétés pharmacologiques. Les bêta-bloquants dits non sélectifs présentent en plus un antagonisme pour les adrénorécepteurs β_2 . Les bêta-bloquants dits cardio-sélectifs ou β_1 sélectifs possèdent une plus grande affinité pour les récepteurs β_1 que pour les récepteurs β_2 . Les bêta-bloquants entraînant une activation partielle des récepteurs β sont dits à activité sympathomimétique intrinsèque (ISA). Certains possèdent également des propriétés additionnelles vasodilatatrices (Table 3). Ces propriétés pharmacologiques secondaires entraînent des variations dans la capacité de chacun à induire des PV. Nous avons donc essayé de mettre en évidence cette différence. Pour ce faire nous avons choisi de réaliser une méta-analyse en réseau (NMA). Cette approche récente permet de prendre en compte plusieurs traitements simultanément et non deux à deux comme dans une méta-analyse simple et donc de hiérarchiser un effet au sein d'un groupe. Elle inclut des comparaisons directes et indirectes entre chaque traitement et prend donc en compte l'ensemble des preuves disponibles pour quantifier un effet relatif ; elle augmente la puissance grâce à ces comparaisons indirectes et permet des comparaisons peu ou

pas réalisées en pratique. Nous avons inclus dans cette NMA tous les essais cliniques contrôlés randomisés de la base de données PubMed, en extrayant pour chacun d'eux la prévalence de PR ou de symptômes associés (froideur des extrémités, ischémie périphérique...) s'ils étaient renseignés. Nous avons de plus inclus certaines références pertinentes de la Cochrane Library, de Google scholar et du Trialresultcenter (Figure 2). Différents objectifs secondaires ont également été poursuivis : l'influence de la latitude, du moyen de report de l'effet indésirable (questionnaire, report spontané, visite médicale...), du critère clinique rapporté (syndrome de Raynaud ou froideur des extrémités), de la pathologie sous-jacente, de la dose et de la durée de traitement, et enfin de l'année de publication sur la prévalence de PV.

Nous avons donc identifié 2238 articles correspondant à nos critères, 829 d'entre eux ont été sélectionnés afin de rechercher un effet indésirable en relation avec une PV. Finalement 38 études renseignaient un effet indésirable pertinent et regroupait plus de 57000 patients.

Treize bêta-bloquants ont été comparés, entre eux, contre placebo et versus autres traitements actifs (le plus souvent des inhibiteurs de l'enzyme de conversion, des antagonistes des récepteurs de l'angiotensine, des α bloquants et des dihydropyrimidines). La prévalence de PV au sein des patients traités par bêta-bloquants est de 7% (1966/28072), alors que 4.6% (555/12060) et 1.7% (305/17492) des patients traités par placebo ou autre traitement actif ont développés des symptômes traduisant une PV ($P < 0.001$).

Les résultats de cette étude confirment effectivement l'existence d'une variabilité notoire au sein de la classe de bêta-bloquants. En effet, les risques relatifs (OR) de vasoconstriction périphérique entre les différents bêta-bloquants et placebo sont extrêmement hétérogènes. Seuls l'aténolol, le propranolol et le métoprolol sont associés à une augmentation significative du risque de PV. L'analyse en sous-groupes a également fait ressortir une large disparité de prévalence des PV entre les différents groupes pharmacologiques de bêta-bloquants. Les

vasodilatateurs et les bêta-bloquants possédant une ASI induisent moins de PV que le placebo. Alors que la prévalence de PV dans les groupes des bêta-bloquants β_1 sélectifs et de ceux dépourvus de propriétés secondaires est significativement plus importante que celle retrouvée sous placebo. Le pindolol, bêta-bloquant avec la plus forte ISA, arrive donc logiquement en tête des bêta-bloquants les moins à même d'induire une PV. Il pourrait même être considéré comme un vasodilatateur périphérique. Ces observations sont cohérentes avec d'anciennes études qui avaient retrouvé une augmentation du flux sanguin distal avec les bêta-bloquants possédant une forte ISA, résultats également cohérents avec le mécanisme supposé de cet effet indésirable: l'introduction d'un traitement par bêta-bloquant entraîne une chute du débit cardiaque. Cette dernière induit une inhibition des barorécepteurs aortiques et sino-carotidiens conduisant, via la stimulation des adrénorécepteurs α_1 et α_2 à une augmentation du tonus sympathique et une vasoconstriction périphérique réflexe, vasoconstriction à l'origine des symptômes (Figure 7). Notons que l'implication d'un défaut de régulation de ces récepteurs α_2 constitue l'une des principales hypothèses étiologiques neurovasculaires du PR primaire.

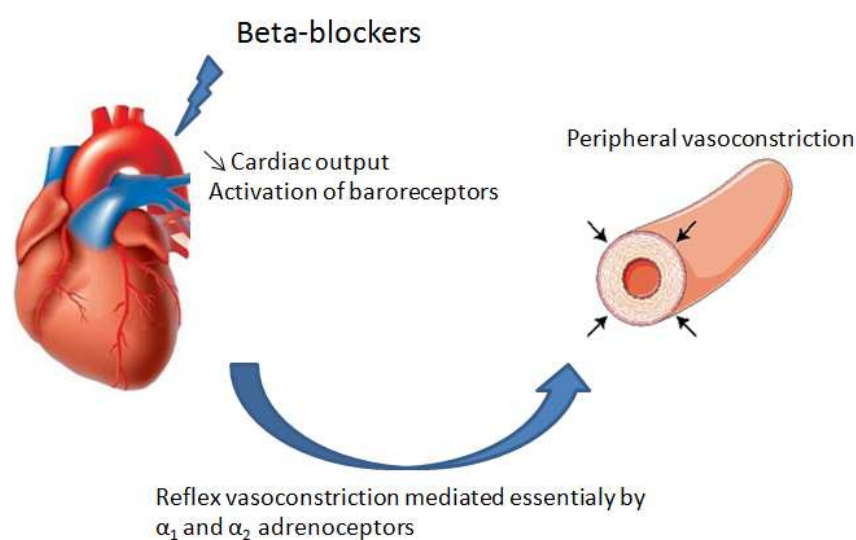


Figure 7. Mécanisme d'action supposé de la vasoconstriction périphérique induite par les bêta-bloquants.

Cette hypothèse physiopathologique est également corroborée dans notre étude par le fait que les deux bêta-bloquants possédant une propriété α_2 bloquante (acébutolol et labétalol) sont, au même titre que les bêta-bloquants avec une ISA, les moins pourvoyeurs de PV. Quant au carvedilol, il possède lui aussi une activité α_2 bloquante mais le peu d'études et d'effectifs, entraînant une très large imprécision de l'estimation, ne permettent pas de conclure.

Une baisse de la mesure du flux sanguin distal, une augmentation des plaintes liées à une froideur des extrémités et des cas de PR ont été décrits dans la littérature chez des patients sous bêta-bloquants. Malgré cela aucune étude n'a réussi à montrer une plus grande fréquence ou sévérité des crises de PR suite à la prise de bêta-bloquants chez les patients atteints de PR primaire. Le PR est cependant un syndrome complexe, impliquant un grand nombre de mécanismes.

Les objectifs secondaires que nous poursuivions ont donné lieu à des méta-régressions qui n'ont pas été significatives.

La qualité des résultats a été évaluée selon des recommandations récentes appelées GRADE. Celles-ci ont pour but de donner un avis sur la fiabilité de chaque comparaison directe, indirecte ou mixte faisant partie de notre réseau. Cinq axes devant donner lieu à un jugement doivent être évalués pour chaque comparaison : « risk of bias, inconsistency, indirectness, imprecision and publication bias ». Le plus haut score de fiabilité méthodologique est donné à une étude contrôlée randomisée puis ce score est pondéré par les différents biais potentiels identifiés. Cette méthode intéressante bien que fastidieuse a été assez flexible pour s'adapter à notre objectif qui avait pour but d'évaluer la sécurité d'emploi des bêta-bloquants et non leur efficacité. Parmi nos 34 comparaisons directes, 7 sont considérées comme fiables et 7 autres comme de mauvaise qualité. Cet outil permet de poser les bases de l'évaluation de la qualité d'une preuve établie par une méta analyse en réseau mais le résultat nous paraît peu lisible et

complexe à analyser. De nouvelles recommandations viennent d'être développées et doivent être mises en pratique afin d'évaluer leur faisabilité et leur fiabilité (201). Ces recommandations permettront à terme une harmonisation et une standardisation des pratiques, nécessaires devant l'utilisation croissante de ce modèle de NMA.

Ces résultats permettent de soulever la question de la pertinence des contre-indications des différents bêta-bloquants chez les patients atteints de PR. En effet, en France, le carvedilol, le nadolol, l'oxprénolol, le pindolol, le propranolol et le sotalol sont contre-indiqués chez tous les patients atteints de PR; les bêta-bloquants β_1 selectifs (l'acébutolol, le bétaxolol, le bisoprolol, le métoprolol, le nébivolol) uniquement dans les formes sévères; alors que le céliprolol et le labétalol ne sont pas contre indiqués. A la lumière de ces observations ces recommandations ne nous paraissent pas pertinentes et en inadéquation avec l'influence des propriétés secondaires des bêta-bloquants sur leur capacité d'induction de RP.

MEMOIRE SOUTENU PAR : M. Khouri Charles

TITRE : Le phénomène de Raynaud iatrogène : revue de la littérature et méta- analyse en réseau des vasoconstrictions périphériques induites par les bêtabloquants.

Conclusion

L'iatrogénie médicamenteuse représente une des principales étiologies du phénomène de Raynaud (PR) secondaire. L'étiologie médicamenteuse du PR est cependant mal connue et probablement sous-estimée. Souvent bénin le PR peut dans ces formes secondaires, plus sévères, induire l'apparition d'ischémies et d'ulcères digitaux. De nombreuses classes médicamenteuses sont suspectées d'induire ou d'aggraver des PR préexistants. Nous n'avons cependant que peu de certitudes quant à leur prévalence, la présentation clinique associée à chaque classe médicamenteuse et leur physiopathologie. Afin de répondre à ces questions nous avons donc mené une revue de la littérature, qui nous a permis de regrouper les classes médicamenteuses par mécanisme physiopathologique, d'apprécier la prévalence des PR induits par les médicaments ainsi que leur gravité potentielle. Néanmoins, le niveau de preuve de l'association entre la survenue de PR et ces médicaments est souvent faible pour la plupart d'entre eux, et peu d'études de bonne qualité méthodologique ont été réalisées.

L'exemple des bêtabloquants est frappant ; bien que ce soit l'une des premières classes médicamenteuses à avoir été liée à l'apparition de PR, sa prévalence est mal connue et de nombreuses questions restent en suspens, notamment l'influence de leurs propriétés pharmacologiques secondaires. Le paradoxe est que des milliers d'essais cliniques incluant des bêtabloquants ont été publiés dans la littérature ces dernières décennies.

Nous avons donc réalisé une méta-analyse en réseau, approche qui combine comparaisons directes et indirectes afin de hiérarchiser différentes molécules au sein d'une même classe de médicaments. Parmi les 2238 références retrouvées, 38 études ont été incluses dans l'analyse. Celle-ci nous a permis de mettre en évidence une hétérogénéité au sein de la classe des bêtabloquants, avec un effet positif de l'activité sympathomimétique intrinsèque, alors que la sélectivité β_1 n'avait pas d'influence sur la survenue de PR. Ces résultats remettent en cause la pertinence des précautions d'emploi et des contre-indications de certains bêtabloquants chez les patients atteints de PR.

Ce travail montre que la méta-analyse réseau est une approche intéressante dans le domaine de la pharmacovigilance, pour quantifier et hiérarchiser la survenue d'effets indésirables au sein d'une classe de médicaments. Néanmoins, beaucoup de travail nous semble encore nécessaire à afin de progresser dans la compréhension du PR iatrogène et de pouvoir améliorer le diagnostic précoce et la prise en charge de cet effet indésirable.

(*) VU ET PERMIS D'IMPRIMER

(*) Grenoble, le 8 juin 2015

(*) LE DOYEN

(*) LE PRESIDENT DE THESE

(*) PROFESSEUR C. RIBUOT

(*) PROFESSEUR C. RIBUOT



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**Annexe 1 : Pharmacologie du phénomène de Raynaud, Thérapie 2014
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Pharmacologie du phénomène de Raynaud

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Résumé – Le phénomène de Raynaud (PR) correspond à une ischémie paroxystique des extrémités en réponse à un stress environnemental. Il est dit primaire lorsqu'il est idiopathique, et secondaire lorsqu'il est associé à certaines pathologies responsables d'une oblitération vasculaire. Bien que sa physiopathologie soit complexe et imparfaitement connue, la dysfonction microvasculaire joue un rôle clé dans la survenue du PR. Cette revue de la littérature synthétise les différents traitements pharmacologiques actuellement utilisés dans le PR, en abordant leur mécanisme d'action et le niveau de preuve de leur efficacité. Nous discuterons également de nouvelles pistes pharmacologiques comme la potentialisation de la voie du monoxyde d'azote ou l'inhibition de la voie RhoA-Rho kinase. L'autre aspect de la pharmacologie du PR abordé dans cette revue est l'étiologie médicamenteuse de certaines formes secondaires. Parmi les médicaments incriminés on retrouve notamment les bêta-bloquants, les interférons, certaines chimiothérapies anticancéreuses ou plus récemment des inhibiteurs de tyrosine-kinases.

Abstract – Pharmacology of Raynaud's Phenomenon. Raynaud's phenomenon (RP) is characterised by transient ischaemia in the extremities in response to cold or emotions. It can be primary (idiopathic) or secondary to an underlying disease. The pathophysiology of RP is multifactorial and complex. Microvascular impairment is a hallmark of the disease. The objective of this work is to review the different pharmacological treatments currently used in the management of RP, from their mechanism of action to the available evidence regarding their efficacy. We also propose to discuss potential pharmacological targets such as the potentiation of the nitric oxide pathway, or the inhibition of the RhoA-Rho kinase pathway. The last part of this review deals with drug-induced RP. Among various medications, beta-blockers, interferons, tyrosine-kinase inhibitors or cytotoxic agents such as bleomycin are involved.

Abréviations : voir en fin d'article.

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Serment de Galien



« Je jure en présence des Maîtres de la Faculté, des Conseillers de l'Ordre des Pharmaciens et de mes condisciples :



D'honorer ceux qui m'ont instruit(e) dans les préceptes de mon art et de leur témoigner ma reconnaissance en restant fidèle à leur enseignement.



D'exercer, dans l'intérêt de la santé publique, ma profession avec conscience et de respecter non seulement la législation en vigueur, mais aussi les règles de l'honneur, de la probité et du désintéressement.



De ne jamais oublier ma responsabilité et mes devoirs envers le malade et sa dignité humaine ; en aucun cas, je ne consentirai à utiliser mes connaissances et mon état pour corrompre les mœurs et favoriser des actes criminels.



Que les hommes m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert(e) d'opprobre et méprisé(e) de mes confrères si j'y manque ».