ISSN 2220-3214 (online)

World Journal of *Rheumatology*

World J Rheumatol 2012 October 3; 2(2): 12-26

Baishideng Publishing Group
www.wjgnet.com

WJR World Journal of Rheumatology

A peer-reviewed, online, open-access journal of rheumatology

Editorial Board

2011-2015

The *World Journal of Rheumatology* Editorial Board consists of 116 members, representing a team of worldwide experts in rheumatology. They are from 29 countries, including Argentina (1), Australia (4), Belgium (2), Canada (2), China (11), Finland (2), France (6), Germany (4), Greece (6), Hungary (2), India (3), Iran (2), Israel (4), Italy (5), Japan (1), Mexico (2), Morocco (2), Netherlands (1), Peru (1), Slovakia (1), South Korea (4), Spain (4), Sweden (1), Switzerland (1), Thailand (1), Tunisia (1), Turkey (13), United Kingdom (8), and United States (21).

WJR World Journal of Rheumatology

Contents

Bimonthly Volume 2 Number 2 October 3, 2012

World Journal of Rheumatology
Volume 2 Number 2 October 3, 2012

Contents

NAME OF JOURNAL
World Journal of Rheumatology

ISSN
ISSN 2220-3214 (online)

LAUNCH DATE
December 31, 2011

FREQUENCY
Bimonthly

EDITING
Editorial Board of *World Journal of Rheumatology*
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: wjrheumato@wjgnet.com
http://www.wjgnet.com

EDITOR-IN-CHIEF
Jörg HW Distler, MD, Department of Internal Medicine 3, University of Erlangen-Nuremberg, Universitätsstr, 29, 91054 Erlangen, Germany

EDITORIAL OFFICE
Jian-Xia Cheng, Director
Jin-Lei Wang, Vice Director
World Journal of Rheumatology
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-8538-1893
E-mail: wjrheumato@wjgnet.com
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Co., Limited
Room 1701, 17/F, Henan Building,
No.90 Jaffe Road, Wanchai, Hong Kong, China
Fax: +852-31158812
Telephone: +852-58042046
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

PUBLICATION DATE
October 3, 2012

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/2220-3214/g_info_20100722180909.htm

ONLINE SUBMISSION
http://www.wjgnet.com/esps/

World Journal of Rheumatology

Online Submissions: http://www.wjgnet.com/esps/
wjrheumato@wjgnet.com
doi:10.5499/wjr.v2.i2.12

World J Rheumatol 2012 October 3; 2(2): 12-20
ISSN 2220-3214 (online)

TOPIC HIGHLIGHT

Mónica Vazquez del Mercado, MD, *Series Editor*

Pulmonary arterial hypertension associated with systemic sclerosis: Current diagnostic approach and therapeutic strategies

Olga Vera-Lastra, Mateo Porres-Aguilar

Olga Vera-Lastra, Department of Internal Medicine, Hospital de Especialidades, Centro Médico Nacional la Raza, IMSS, Universidad Nacional Autónoma de México, 02990 Mexico City, México
Mateo Porres-Aguilar, Division of Hospital Medicine, Department of Internal Medicine, Texas Tech University Health Sciences Center/Paul L. Foster School of Medicine, El Paso, TX 79905, United States
Author contributions: Vera-Lastra O and Porres-Aguilar M contributed equally in the design and writting of this work.
Correspondence to: Olga Vera-Lastra, MD, Department of Internal Medicine, Hospital de Especialidades, Centro Médico Nacional la Raza, IMSS, Universidad Nacional Autónoma de México, Seris y Saachila s/n, colonia La Raza, 02990 Mexico City, México. olgavera62@yahoo.com.mx
Telephone: +52-55-57245900 Fax: +52-55-57245900
Received: September 28, 2011 Revised: December 23, 2011
Accepted: July 5, 2012
Published online: October 3, 2012

Abstract

Pulmonary arterial hypertension (PAH) represents a devastating vascular complication of systemic sclerosis (SSc) and is found in 10%-15% of cases carrying a severe prognosis. PAH has a dramatic impact on the clinical course and overall survival, being the single most common cause of death in patients with this entity. The clinical course and aggressive progression of PAH has led clinicians to perform annual screening for it, since early detection and diagnosis are the cornerstone of a prompt therapeutic intervention. The diagnosis of PAH can be challenging to clinicians, particularly in its early stages, since in the context of SSc, the multiple causes of dyspnea need to be assessed. Doppler echocardiography represents the best initial screening tool, however, right heart catheterization remains the gold standard and definitive diagnostic means. Remarkable advances have been achieved in elucidating the pathogenesis of PAH in the past two decades, leading to the development of disease-specific targeted therapies: prostacyclin analogues, endothelin receptor antagonists and inhibitors of five phosphodiesterase pathways. However, the clinical response to these therapies in SSc-associated PAH has not been as great as the one seen with idiopathic PAH. This review also focuses on the diagnosis and novel therapies that are currently available for PAH, as well as potential future therapeutic developments based on newly acquired knowledge of diverse pathogenic mechanisms.

Key words: Pulmonary arterial hypertension; Systemic sclerosis; Diagnosis; Therapy; Prognosis

Peer reviewer: Dr. Allison B Reiss, Department of Medicine, Vascular Biology Institute, Winthrop University Hospital, 222 Station Plaza, North Mineola, NY 11501, United States

Vera-Lastra O, Porres-Aguilar M. Pulmonary arterial hypertension associated with systemic sclerosis: Current diagnostic approach and therapeutic strategies. *World J Rheumatol* 2012; 2(2): 12-20 Available from: URL: http://www.wjgnet.com/2220-3214/full/v2/i2/12.htm DOI: http://dx.doi.org/10.5499/wjr.v2.i2.12

INTRODUCTION

Pulmonary arterial hypertension (PAH), hemodynamically defined as a mean pulmonary arterial pressure (mPAP) greater than 25 mmHg, a mean pulmonary capillary wedge pressur < 15 mmHg, and pulmonary vascular resistance greater than 3 Wood units, represents a progressive syndrome of the pulmonary vasculature that leads to progressive right ventricular failure, long-term disability

and often death if left untreated within 2-2.5 years[1,2]. Systemic sclerosis (SSc) is defined as a heterogeneous disorder characterized by endothelial dysfunction, dysregulation of fibroblasts resulting in excessive production of collagen, and abnormalities in the immune system[3,4]. These processes lead to progressive fibrosis of the skin and internal organs resulting in premature organ failure and death. Pulmonary involvement in SSc include interstitial lung disease (ILD) and PAH, which are the most common pulmonary manifestations nowadays and are now the leading causes of death in SSc[5]. Typically, SSc-associated PAH (SSc-PAH) will develop in patients with a limited form of SSc after 10-15 years of evolution of the disease[6,7].

The frequency of SSc-PAH is about 8%-15% depending on the diagnostic method used. The following methods have been recommended for its diagnosis, treatment-follow-up and prognosis: Doppler transthoracic echocardiogram (TTE), complete pulmonary function tests (PFTs) or spirometry including carbon monoxide diffusing capacity (DLCO), the 6 min walk test (6MWT), and biological markers: n-terminal pro-brain natriuretic peptide (NT-pro-BNP). The right heart catheterization (RHC) remains the gold standard for definitive diagnosis of PAH[8-10].

Remarkable advances have been achieved in elucidating the pathogenesis of PAH over the past two decades, leading to the rapid development of disease-specific therapies. However, despite these achievements, the response to therapies is often divergent and suboptimal in the subgroup of patients with SSc-PAH, since survival remains poor, particularly when compared with idiopathic PAH (IPAH)[11].

PATHOGENESIS AND PATHOBIOLOGY

Endothelial dysfunction plays an essential role in the pathogenesis of SSc-PAH, which histopathologically is characterized by intimal hyperplasia, medial hypertrophy, and adventitial fibrosis. These changes lead to the development of concentric obliterative arteriolar vasculopathy with angioproliferative plexiform lesions; however, there are fewer plexiform lesions, increased intimal fibrosis, and more heterogeneity when compared with lesions in IPAH[12]. Two recent histopathological studies have demonstrated the presence of pulmonary veno-occlusive disease characterized by fibrotic remodeling of post-capillary venules and preseptal veins, however, this needs to be confirmed in larger studies[12].

Autoimmunity appears to play a central role in pulmonary vascular remodeling. These include endothelial cell apoptosis and activation with expression of cell adhesion molecules, inflammatory cellular recruitment, hypercoagulable state, and intimal proliferation and adventitial fibrotic changes leading to obliterative arteriolopathy[13,14]. Several studies have demonstrated increased circulating factors like the soluble vascular cell adhesion molecule, consistent with endothelial cell injury[15]. Dysregulated angiogenesis may play also an important role in the development of SSc-PAH, reflected by increased levels of circulating vascular endothelial growth factor (VEGF)[16].

Autoantibodies are often associated with the development of certain phenotypes in SSc with the subsequent development of PAH. Antifibrillarin antibodies are frequently found in SSc-PAH patients and the antiendothelial cell antibodies correlate with digital ischemia and infarcts, and could display distinct reactivity profiles against antigens from the micro and macrovascular beds[17,18].

Given the importance of the concept of vasoproliferation and endothelial dysfunction described in different forms of PAH[19,20], it has also been hypothesized in SSc-PAH: an imbalance of vasomediators leading to vasoconstriction, endothelial damage leading to further vascular remodeling, proliferation of the endothelium and vascular smooth muscle cells, along with *in situ* thrombosis[19,20]. Increased levels of endothelin type-1 (ET-1), a potent selective pulmonary vasoconstrictor produced in the pulmonary vascular endothelium, has been shown to play a prominent role in the pathobiology of PAH[20]. Both serotonin and ET-1 are dual-action potent pulmonary vascoconstrictors that may induce significant pulmonary vascular remodeling change as well as mitogenic changes in the pulmonary arterioles[21,22]. At the same time, synthesis of vasodilators such as nitric oxide (NO) and prostacyclin may be decreased in different forms of PAH, facilitating further the vascular remodeling and the proliferative response. Importantly, prostacyclin synthase levels have been demonstrated to be down-regulated in patients with PAH[23].

DIAGNOSTIC APPROACH

Clinical presentation

Typically, patients with SSc-PAH are predominantly women, have limited SSc, and tend to be older. Clinical symptoms in PAH tend to be nonspecific, and dyspnea on exertion is the most common initial complaint[1,19-22]. Other common symptoms include fatigue, generalized weakness, light-headedness, and orthopnea. Physical examination may show elevated jugular venous pressure in the neck, an accentuated pulmonic component of the second heart sound, a systolic murmur that could be consistent with tricuspid regurgitation or a murmur of pulmonic insufficiency (Graham-Steele murmur), as well as a pulsatile liver, suggestive of hepatic congestion. Dependent bilateral lower extremity edema may be a sign of right ventricular dysfunction and PAH[20]. In addition, since other organs could be commonly affected in SSc, including myocardial, pericardial, or generalized vascular and musculoskeletal organs, causing also the above mentioned myriad of symptoms, the initial diagnostic approach represents a complete challenge for the clinician. Furthermore, patients with SSc-PAH more commonly present with pericardial effusion when compared with IPAH, although it remains unclear whether the effusions

are due to progressive right ventricular (RV) dysfunction or due to the underlying autoimmune process.

Specific screening and assessment

Patients with SSc have an advantage over IPAH patients, since SSc patients (both limited and diffuse SSc) are identified as a population at high risk to develop PAH overtime. Therefore, we recommend close clinical surveillance as well as annual screening by useful tools that we will discuss in the latter section of this review, particularly screening for pulmonary complications like ILD and/or PAH. This constitutes an annual or biannual Doppler TTE, complete PFTs or spirometry including DLCO and the 6MWT[24]. A recently published consensus statement from the American College of Cardiology, American Heart Association in conjunction with the American College of Chest Physicians (ACCP), American Thoracic Society and the Pulmonary Hypertension Association strongly recommends yearly TTE for patients with SSc to screen for PAH[24].

PFTs abnormalities, such as progressive decline in DLCO, alone or in combination of a forced vital capacity (FVC)%/DLCO% ratio > 1.4 may identify SSc patients that could be developing PAH, however, this strategy may not be routinely performed by clinicians[6,25,26]. Hormonal and humoral dysfunction is also common in PAH, as evidenced by signs of neurohormonal activation by elevated levels of NT-pro-BNP, a neuropeptide released in response to right ventricular stretch and stress, is frequently elevated in SSc-PAH and appears significantly higher than in patients with IPAH despite similar hemodynamic alterations[27]. Simultaneously, hyponatremia, a marker of neurohormonal activation, is also very common in SSc-PAH, and portends a poor prognosis[28].

The 6MWT is employed as a simple, reproducible, and valid measure of submaximal cardiopulmonary exercise capacity. The utility of the test as a predictor of prognosis, and measure of response to pharmacological therapy has been well studied and validated. The test has also been used as a surrogate to predict survival and utilized as a primary outcome in pharmacological PAH clinical trials and has also been well studied and prospectively validated in the IPAH subgroup[29]. However, its value in the evaluation of submaximal exercise capacity in SSc-PAH has become a great matter of debate, since in this subset of patients their functional status is not only affected by the cardiorespiratory status, but also arthropathy, myopathy, musculoskeletal dysfunction or lower extremity digital ischemia associated with SSc[30]. Hence, the 6MWT does not always represent a reliable tool when evaluating the cardiopulmonary capacity in SSc-PAH patients, limiting its utility[31].

NT-pro-BNP represents an acceptable serum marker for severity, prognosis, and response to therapy in patients with different forms of PAH[32]. However, in SSc, subclinical myocardial involvement is common and NT-pro-BNP can be elevated in patients with early myocardial involvement, as well as in SSc-PAH[33]; moreover, elevated NT-pro-BNP does not help differentiate left heart disease from right ventricular systolic or diastolic dysfunction in the setting of SSc, especially when both pathophysiological entities coexist[33].

TTE represents an essential, probably the best non-invasive method of choice for the initial assessment and screening tools in the diagnostic approach for diverse forms of PAH[1,8,19-22]. In a large multicenter French study, patients with SSc and non severely depressed FVC by PFTs, were screened using Doppler TTE; those with a tricuspid regurgitation velocity (TRV) jet > 3 m/s, or 2.5-3 m/s accompanied by unexplained dyspnea, underwent RHC to confirm PAH[7]. This study supported the idea that proper screening may help identify patients at an early stage of their disease. TTE is useful because it can help in the differential diagnosis of pulmonary hypertension, identifying elevated pulmonary arterial pressures due to systolic and diastolic left ventricular dysfunction. Several indices of right ventricular function, such as the tricuspid annular plane systolic excursion (TAPSE) and the right ventricular systolic performance index (Tei index), can also be determined by this technique[34,35]. Acknowledging the limitations of TTE for the definitive diagnosis of PAH, the echocardiographic estimation of the likelihood of PAH is among the key elements in the decision-making process, related to the need and timing of RHC in patients with suspected PAH. A retrospective analysis assessed 137 SSc patients regardless of the presence or absence of ILD. The cut off from the estimated right ventricular systolic pressure (RVSP) of 35 mmHg and the TRV jet of 2.75 m/s had an 88% sensitivity and 42% specificity for the diagnosis of PAH[36]. A cut off of RVSP > 50 mmHg and TRV jet > 3.3 m/s had 97% specificity but only 47% of sensitivity for the diagnosis of PAH[36].

Frea *et al*[37] prospectively studied 38 patients with SSc without PAH during a 12 mo period including TTE evaluation, calculating RV function and morphology, TRV jets, RVSP, TAPSE, Tei index, and pulmonary flow acceleration time (AcT), as well as RV outflow tract time-velocity integral (TVI), and found that four patients developed PAH. Only TRV/AcT and TRV/TVI ratios significantly predicted the development of PAH, showing good diagnostic power (TRV/TVI ratio with 75% sensitivity and 95% specificity and TRV/AcT ratio with 75% sensitivity and 71% specificity). The multicenter pulmonary hypertension assessment and recognition of outcomes in scleroderma registry prospectively follows patients with SSc at high risk or with incidental PAH. Analyses of this multinational registry will allow identification of risk factors for the development of PAH among SSc patients and enhance understanding of the course of SSc-PAH[38].

The ongoing detecting early tumors enables cancer therapy study in SSc patients is currently evaluating prospectively the role of TTE against RHC for sensitivity, specificity, predictive value in identifying patients with PAH[39].

RHC assessing cardiopulmonary hemodynamics represents the gold standard and is necessary for the definitive diagnosis of PAH[1,2,8]. Mean right atrial pressure, decreased cardiac index (CI), and increased mPAP are predictors of death or need for lung transplantation in IPAH[24]. However, although these data have been prospectively validated in the IPAH subgroup of patients, they remain of unclear usefulness in SSc-associated PAH patients. In a retrospective analysis comparing baseline hemodynamic parameters between IPAH and SSc-PAH patients, patients with SSc had significantly lower mPAP and pulmonary vascular resistance by RHC and equally depressed CI compared with IPAH patients; however, follow-up demonstrated that SSc patients were four times more likely to die when compared with IPAH patients despite comparable therapy[7]. These paradoxical findings suggest that the RV may have a reduced ability to adapt to increased mPAP, perhaps related in part due to myocardial involvement in SSc.

The Johns Hopkins Pulmonary Hypertension Center of Excellence has recently developed and proposed a diagnostic algorithm for routine clinical tests and tools in patients with SSc, which may allow early detection of PAH, as well as other potential causes of dyspnea such as myocardial involvement (left ventricular dysfunction), as well as diffuse parenchymal lung disease such as ILD[40] (Figure 1).

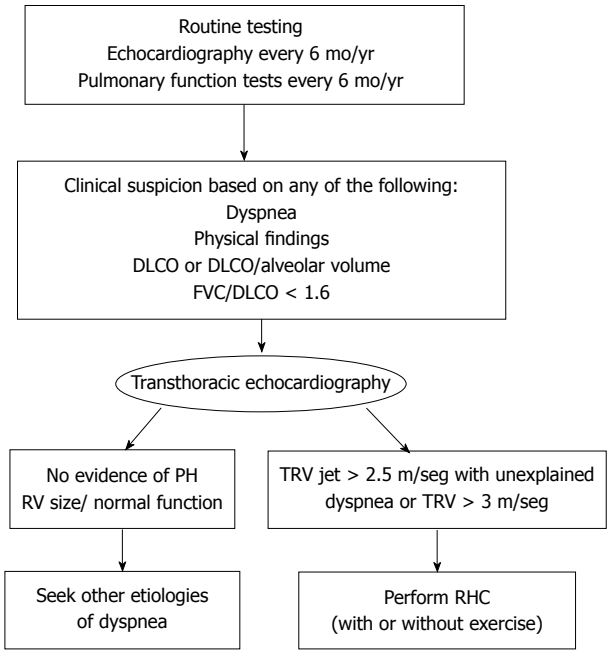

Figure 1 Algorithm for detection of pulmonary arterial hypertension in patients with systemic sclerosis. Proposed algorithm for performance of routine clinical tests in patients with systemic sclerosis, which may allow early detection of pulmonary arterial hypertension or other causes of cardiac dysfunction (e.g. left ventricular diastolic or systolic dysfunction). DLCO: Diffusing capacity of carbon monoxide; FVC: Forced vital capacity; PH: Pulmonary hypertension; RHC: Right heart catheterization; RV: Right ventricle; TRV: Tricuspid regurgitation velocity. Reproduced with permission from Hassoun[40].

TREATMENT

A better understanding of the pathophysiologic mechanisms in PAH, has allowed clinicians to develop new and effective therapeutic targets for this devastating disease[41-43]. Currently, three main classes of drugs for the treatment of PAH exist: prostacyclin analogues, endothelin receptor antagonists (ETRA) and phosphodiesterase type 5 inhibitors (PDEI-5)[44].

Prostacyclin analogues

Prostacyclin and its analogues are metabolites of the arachidonic acid that are produced by the vascular endothelium. They exhibit potent vasodilatory, antithrombotic, antiproliferative and anti-inflammatory properties. The vasoconstriction, thrombosis, proliferation and the lack of endogenous prostaglandin I-2 (PGI-2) associated with PAH may contribute substantially to this condition[45]. PAH shows low levels of PGI-2 thus, several analogues have been developed for its management.

Intravenous epoprostenol was the first approved drug for the treatment of PAH, especially for patients with functional class Ⅳ and advanced right ventricular failure. Treatment with epoprostenol was associated with improvement in exercise capacity, hemodynamic measures and quality of life not only in patients with IPAH, but also in patients with PAH-SSc[46,47]. Intravenous epoprostenol has been approved by the Food and Drug Administration for the treatment of severe IPAH, supported by the results of randomized controlled trials (RCT) which have documented significant improvement in the survival of these patients[48,49]. Therefore, it is recommended for the treatment of IPAH as well as for severe SSc-PAH[50].

Treprostinil (subcutaneous, intravenous or inhalation), iloprost (intravenous or inhaled) and beraprost (oral) are other PGI-2 analogues with longer half-life which were developed later, and can be administered by different routes and have also proved effective in the treatment of PAH. Subcutaneous treprostenil has been studied in a large RCT of 470 patients with PAH, which included patients with connective tissue disease (CTD-PAH), where it was found to improve exercise capacity 6WMT, hemodynamics and clinical events[51]. A post-hoc analysis of data from 90 patients with CTD-PAH including SSc-PAH demonstrated that continuous subcutaneous infusion of treprostenil improved exercise capacity, symptoms of PAH and pulmonary hemodynamic parameters[52].

Studies suggested that inhaled iloprost, a stable PA, promotes selective pulmonary vasodilatation, improves hemodynamics and exercise capacity in patients with PAH. This medication was investigated in 203 patients, 17 of whom had CTD-PAH and it was concluded that there was an improvement in 6WMT in patients who received inhaled iloprost *vs* deterioration in those who received placebo[53]. Inhaled iloprost is an effective therapy for patients with severe PAH. An uncontrolled study in SSc-PAH patients treated with aerosolized iloprost showed it is potentially useful as a treatment for these patients[54].

ETRA

ETRA have proven useful in patients with IPAH and with CTD-PAH, especially SSc. PAH is characterized by excess production of endothelin-1 (ET-1), therefore blocking the effects of ET-1 *via* antagonism of the ET_A and ET_B receptors is an important therapeutic strategy[41]. Three molecules are currently available for the treatment of PAH. Bosentan, which non-selectively blocks both ET_A and ET_B receptors, sitaxsentan and ambrisentan, which selectively blocks the ET_A receptor[41,55]. Two RCTs demonstrated that bosentan improves exercise capacity, functional class and some hemodynamic measures in PAH[56,57].

Denton *et al*[58] published a subgroup analysis on the use of bosentan in the treatment of severe CTD-PAH including SSc-PAH. This study found that short-term treatment with bosentan seemed to have a favorable effect compared with placebo.

The long-term follow-up of these patients suggests that bosentan, plus other PAH treatments, if required, is safe for long-term treatment and may have a positive effect on patient outcome. The 92% estimate for survival at 48 wk is a significant achievement in this patient population[59]. A retrospective study showed that bosentan in patients with SSc-PAH and IPAH with a follow up of at least 6 mo was associated with long term improvement in functional class and good survival in patients with functional class Ⅲ IPAH. However, most SSc-PAH patients experienced stability and some showed impairment in functional class who tended to have a higher mortality[60]. Analysis of the two RTC and their long-term extension studies suggested that bosentan may improve survival in SSc-PAH in comparison with historic controls[61,62]. Based on the results of RCT, bosentan was recommended in the current guidelines of the ACCP[42].

The new selective ETRA sitaxsentan and ambrisentan have also shown to be efficacious in the treatment of PAH, resulting in small gains in 6MWT and other clinical markers[63]. Studies with these agents which included patients wich SSc-PAH, revealed their efficacy in the treatment of PAH[64]. Sitaxsentan has been studied in two RCT of which STRIDE-2 is the most important. In this study which included 74 patients with CTD-PAH, treatment with sitaxsentan led to improvement in 6WMT over the 18 wk treatment period[64], with a low incidence of hepatic toxicity. Supported by two RCT studies, results indicate that sitaxentan improved exercise capacity, functional class and some hemodynamic measures in PAH. At present, sitaxentan may also be considered in the treatment of SSc-PAH[62,64,65]. Ambrisentan was evaluated in two double-blind studies in 64 patients with IPAH or CTD-PAH, during 12 wk. Their results appeared to improve exercise capacity, symptoms, and hemodynamics in patients with PAH and the incidence and severity of liver enzyme abnormalities was also low[66].

Phosphodiesterase-5 inhibitors

NO works *via* the cyclic guanosine monophosphate (cGMP) pathway to mediate vasodilation and antiproliferation. In PAH there is impaired NO production. Sildenafil inhibits phosphodiesterase type 5 (an enzyme that metabolizes cGMP), thereby enhancing the cGMP mediated relaxation and growth inhibition of vascular smooth-muscle cells, including those in the lung. In a post-hoc subgroup analysis of 84 patients with CTD-PAH in sildenafil use in pulmonary arterial hypertension-1 (45% of the patients had SSc), sildenafil revealed improvement in exercise capacity, hemodynamic and functional class after 12 wk of treatment. Side effects of sildenafil included headache, flushing and heartburn, among the most common[67,68]. Tadalafil is another PDEI-5 that should be used in the treatment of PAH. In patients with PAH, tadalafil 40 mg was given orally and was well tolerated and improved exercise capacity and quality of life measures and reduced clinical worsening[41,69] although further studies are necessary for the treatment of SSc-PAH.

Combination therapy

Based on current knowledge regarding the complex pathobiology involved in the development of PAH, it has been proposed that combined therapy (CT) can provide synergistic effects on the pulmonary vasculature. Presently, CT has been used in treating patients whose response to monotherapy was very poor. The best results can be achieved by either the simultaneous administration of two or more agents or either by the sequential addition of one or more agents to ongoing therapy[70]. Despite the encouraging results in the treatment of IPAH, there is scant information about its use in patients with SSc-PAH[41].

Adding inhaled iloprost to patients receiving bosentan has shown to be beneficial in a small RCT study. In this study, CT was well tolerated and led to an improvement in New York Heart Association (NYHA) functional class, functional class, mPAP and delayed time to clinical worsening[71].

Another study showed that the addition of oral sildenafil to intravenous epoprostenol improved exercise capacity, hemodynamic measurements, time to clinical worsening, and quality of life, but not Borg dyspnea score. Increased rates of headache and dyspepsia occurred in the add-on arm. However, this study excluded patients with SSc-PAH[72]. These results have been more encouraging in the treatment of IPAH than SSc-PAH.

On the other hand, the addition of sildenafil after bosentan monotherapy failed to improve NYHA functional class and 6MWT in IPAH and SSc-PAH. Further studies are necessary to evaluate the tolerability, efficacy and safety CT in patients with SSc-PAH[73].

CT of PDEI with ETRA is currently being evaluated. Therapy of PAH is usually started with oral monotherapy, frequently using an ETRA. When the first line therapy is not tolerated, ETRA is substituted by a PDEI. If treatment goals are not achieved with monotherapy, CT could be used. Treatment of SSc-PAH follows the same algorithms as in IPAH[74].

Table 1 Recommendations for the treatment of systemic sclerosis

Type of drugs	Drugs and doses	Study	Results	Strength of recommendation	Ref.
Endothelin receptor antagonists	Bosentan, 62.5 mg twice daily for 4 wk, followed 125 twice daily for 12 wk	2 RCT	Improves exercise capacity, functional class and some hemodynamic measures	A/B	[56,57]
	Sitaxentan, 100 mg/d for 18 wk	STRIDE-2 study group STRIDE-1 study group	Improves exercise capacity, functional class and some hemodynamic measures	A/B	[64,66]
PDEI-5	Sildenafil, 20, 40, 80 mg three times daily for 12 wk	SUPER study group	Improves exercise capacity, functional class and some hemodynamic measures	A/B	[67]
Prostacyclin analogues	Intravenous epoprostenol at the start usually < 2 ng/kg of body weight per minute (infused continuously by infusion pump); during 12 wk study, doses were adjusted with mean epoprostenol infusion rate of 11 ng/kg per minute	RCT	Improves exercise capacity, functional class and hemodynamic measures	A/B	[46]

RCT: Randomized controlled trials; SUPER: Sildenafil use in pulmonary arterial hypertension; STRIDE: Sitaxsentan to relieve impaired exercise; A/B: Based on studies with high levels of recommendation; PDEI-5: Phosphodiesterase type 5 inhibitor.

New therapies: Tyrosine kinase inhibitors

The PAH is characterized by an aberrant proliferation of endothelial, smooth muscle cell, and increased expression of secreted growth factors such as the VEGF and the platelet derived grow factor (PDGF). These pivotal discoveries have changed the views in the treatment of PAH. Two strategies that are presently tested: disruption of PDGF and VEGF signaling pathways Imatinib whose mechanism is to inhibit the Bcr-Abl kinase is the prototypical PDGF receptor signaling inhibitor currently under clinical investigation. Sorafenib is the other drug currently being tested. Their efficacy is due to their dual inhibition of VEGF and PDGF signaling pathways. In experimental models of PAH, imatinib has been tested and shown to be effective[40,75,76]. Some reports have indicated its utility including one in patients with SSc-PAH[77-79]. A Phase Ⅱ study evaluating safety, tolerability and efficacy of imatinib in PAH has been completed. Although the study failed to demonstrate improvement in 6MWD there were statistically significant improvements in hemodynamic measurements. Post hoc subgroup analyses indicate that patients with more hemodynamic impairment may respond better than patients with less impairment[80]. If these new antineoplastic drugs with anti-tyrosine kinase activity can play a role in SSc-HAP or in IPAH remains to be proven[40,75].

Based on the potential role of autoimmunity in SSc-PAH, other therapeutic strategies are being studied such as rituximab, an anti CD 20 therapy that depletes B cell lineages. Lately the transcription factor Fos-related antigen-2 (Fra-2), a member of the activator protein 1 family implicated in transforming growth factor-β and PDGF signaling has been found to be up-regulated in patients with SSc. Due to the fact that Fra-2 causes fibrosis and vascular disease, this factor can be a potential therapeutic target[81].

Lung transplantation

Lung transplantation (LT) is the last option for patients with PAH who fail to respond to medical management. Although, SSc is not an absolute contraindication to LT, these patients often have associated comorbidities and multiorgan involvement, placing them at a high risk for LT with a two-year survival rates in cases of SSc patients adequately screened and detected to have PAH comparable to IPAH patients[40,75,82,83].

Recommendations for the treatment of SSc

The European league against rheumatism and scleroderma trial and research group has recently published the following recommendations for the management of SSc-PAH (Table 1).

CONCLUSION

The SSc-PAH is a devastating complication of SSc, deserving adequate periodic screening and prompt diagnosis that will lead to an early treatment. Currently, despite the advances in the knowledge of the pathophysiologic mechanisms of PAH, treatment with PA, ETRA and PDEI have not been as successful as with IPAH. A better understanding of the pathophysiologic mechanisms of the pulmonary vascular remodeling and its impact on the heart and other vital organs in SSc is of paramount importance and cornerstone in order to develop novel therapies.

REFERENCES

1 **Elliott CG**, Barst RJ, Seeger W, Porres-Aguilar M, Brown LM, Zamanian RT, Rubin LJ. Worldwide physician education and training in pulmonary hypertension: pulmonary vascular disease: the global perspective. *Chest* 2010; **137**: 85S-94S
2 **Humbert M**. Update in pulmonary hypertension 2008. *Am J Respir Crit Care Med* 2009; **179**: 650-656
3 **Jimenez SA**, Derk CT. Following the molecular pathways toward an understanding of the pathogenesis of systemic sclerosis. *Ann Intern Med* 2004; **140**: 37-50
4 **LeRoy EC**, Black C, Fleischmajer R, Jablonska S, Krieg T,

Medsger TA, Rowell N, Wollheim F. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988; **15**: 202-205
5 **Steen VD**, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. *Ann Rheum Dis* 2007; **66**: 940-944
6 **Steen V**, Medsger TA. Predictors of isolated pulmonary hypertension in patients with systemic sclerosis and limited cutaneous involvement. *Arthritis Rheum* 2003; **48**: 516-522
7 **Steen V**. Predictors of end stage lung disease in systemic sclerosis. *Ann Rheum Dis* 2003; **62**: 97-99
8 **Hachulla E**, Gressin V, Guillevin L, Carpentier P, Diot E, Sibilia J, Kahan A, Cabane J, Francès C, Launay D, Mouthon L, Allanore Y, Tiev KP, Clerson P, de Groote P, Humbert M. Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. *Arthritis Rheum* 2005; **52**: 3792-3800
9 **Humbert M**, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaici A, Weitzenblum E, Cordier JF, Chabot F, Dromer C, Pison C, Reynaud-Gaubert M, Haloun A, Laurent M, Hachulla E, Simonneau G. Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med* 2006; **173**: 1023-1030
10 **Hachulla E**, de Groote P, Gressin V, Sibilia J, Diot E, Carpentier P, Mouthon L, Hatron PY, Jego P, Allanore Y, Tiev KP, Agard C, Cosnes A, Cirstea D, Constans J, Farge D, Viallard JF, Harle JR, Patat F, Imbert B, Kahan A, Cabane J, Clerson P, Guillevin L, Humbert M. The three-year incidence of pulmonary arterial hypertension associated with systemic sclerosis in a multicenter nationwide longitudinal study in France. *Arthritis Rheum* 2009; **60**: 1831-1839
11 **Fisher MR**, Mathai SC, Champion HC, Girgis RE, Housten-Harris T, Hummers L, Krishnan JA, Wigley F, Hassoun PM. Clinical differences between idiopathic and scleroderma-related pulmonary hypertension. *Arthritis Rheum* 2006; **54**: 3043-3050
12 **Overbeek MJ**, Vonk MC, Boonstra A, Voskuyl AE, Vonk-Noordegraaf A, Smit EF, Dijkmans BA, Postmus PE, Mooi WJ, Heijdra Y, Grünberg K. Pulmonary arterial hypertension in limited cutaneous systemic sclerosis: a distinctive vasculopathy. *Eur Respir J* 2009; **34**: 371-379
13 **Sgonc R**, Gruschwitz MS, Boeck G, Sepp N, Gruber J, Wick G. Endothelial cell apoptosis in systemic sclerosis is induced by antibody-dependent cell-mediated cytotoxicity via CD95. *Arthritis Rheum* 2000; **43**: 2550-2562
14 **Cerinic MM**, Valentini G, Sorano GG, D'Angelo S, Cuomo G, Fenu L, Generini S, Cinotti S, Morfini M, Pignone A, Guiducci S, Del Rosso A, Kalfin R, Das D, Marongiu F. Blood coagulation, fibrinolysis, and markers of endothelial dysfunction in systemic sclerosis. *Semin Arthritis Rheum* 2003; **32**: 285-295
15 **Denton CP**, Bickerstaff MC, Shiwen X, Carulli MT, Haskard DO, Dubois RM, Black CM. Serial circulating adhesion molecule levels reflect disease severity in systemic sclerosis. *Br J Rheumatol* 1995; **34**: 1048-1054
16 **Hummers LK**, Hall A, Wigley FM, Simons M. Abnormalities in the regulators of angiogenesis in patients with scleroderma. *J Rheumatol* 2009; **36**: 576-582
17 **Okano Y**, Steen VD, Medsger TA Jr. Autoantibody to U3 nucleolar ribonucleoprotein (fibrillarin) in patients with systemic sclerosis. *Arthritis Rheum* 1992; **35**: 95-100
18 **Tamby MC**, Chanseaud Y, Humbert M, Fermanian J, Guilpain P, Garcia-de-la-Peña-Lefebvre P, Brunet S, Servettaz A, Weill B, Simonneau G, Guillevin L, Boissier MC, Mouthon L. Anti-endothelial cell antibodies in idiopathic and systemic sclerosis associated pulmonary arterial hypertension. *Thorax* 2005; **60**: 765-772
19 **Porres-Aguilar M**, Anaya-Ayala JE, Porres-Muñoz M, Bracamontes F. [Pulmonary thromboendarterectomy in patients with chronic thromboembolic pulmonary hypertension]. *Cir Cir* 2007; **75**: 131-138
20 **Porres-Aguilar M**, Zuckerman MJ, Figueroa-Casas JB, Krowka MJ. Portopulmonary hypertension: state of the art. *Ann Hepatol* 2008; **7**: 321-330
21 **Rabinovitch M**. Pathobiology of pulmonary hypertension. *Annu Rev Pathol* 2007; **2**: 369-399
22 **Porres-Aguilar M**, Porres-Munoz M. Progress in the pharmacological management of pulmonary arterial hypertension. *Med Int Mex* 2004; **20**: 208-220
23 **Tuder RM**, Cool CD, Geraci MW, Wang J, Abman SH, Wright L, Badesch D, Voelkel NF. Prostacyclin synthase expression is decreased in lungs from patients with severe pulmonary hypertension. *Am J Respir Crit Care Med* 1999; **159**: 1925-1932
24 **McLaughlin VV**, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J, Harrington RA, Anderson JL, Bates ER, Bridges CR, Eisenberg MJ, Ferrari VA, Grines CL, Hlatky MA, Jacobs AK, Kaul S, Lichtenberg RC, Lindner JR, Moliterno DJ, Mukherjee D, Pohost GM, Rosenson RS, Schofield RS, Shubrooks SJ, Stein JH, Tracy CM, Weitz HH, Wesley DJ. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. *Circulation* 2009; **119**: 2250-2294
25 **Goldberg A**. Pulmonary arterial hypertension in connective tissue diseases. *Cardiol Rev* 2010; **18**: 85-88
26 **Proudman SM**, Stevens WM, Sahhar J, Celermajer D. Pulmonary arterial hypertension in systemic sclerosis: the need for early detection and treatment. *Intern Med J* 2007; **37**: 485-494
27 **Mathai SC**, Bueso M, Hummers LK, Boyce D, Lechtzin N, Le Pavec J, Campo A, Champion HC, Housten T, Forfia PR, Zaiman AL, Wigley FM, Girgis RE, Hassoun PM. Disproportionate elevation of N-terminal pro-brain natriuretic peptide in scleroderma-related pulmonary hypertension. *Eur Respir J* 2010; **35**: 95-104
28 **Forfia PR**, Mathai SC, Fisher MR, Housten-Harris T, Hemnes AR, Champion HC, Girgis RE, Hassoun PM. Hyponatremia predicts right heart failure and poor survival in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2008; **177**: 1364-1369
29 **Rasekaba T**, Lee AL, Naughton MT, Williams TJ, Holland AE. The six-minute walk test: a useful metric for the cardiopulmonary patient. *Intern Med J* 2009; **39**: 495-501
30 **Garin MC**, Highland KB, Silver RM, Strange C. Limitations to the 6-minute walk test in interstitial lung disease and pulmonary hypertension in scleroderma. *J Rheumatol* 2009; **36**: 330-336
31 **Pamidi S**, Mehta S. Six-minute walk test in scleroderma-associated pulmonary arterial hypertension: are we counting what counts? *J Rheumatol* 2009; **36**: 216-218
32 **Warwick G**, Thomas PS, Yates DH. Biomarkers in pulmonary hypertension. *Eur Respir J* 2008; **32**: 503-512
33 **Allanore Y**, Wahbi K, Borderie D, Weber S, Kahan A, Meune C. N-terminal pro-brain natriuretic peptide in systemic sclerosis: a new cornerstone of cardiovascular assessment? *Ann Rheum Dis* 2009; **68**: 1885-1889
34 **Forfia PR**, Fisher MR, Mathai SC, Housten-Harris T, Hemnes AR, Borlaug BA, Chamera E, Corretti MC, Champion HC, Abraham TP, Girgis RE, Hassoun PM. Tricuspid annular displacement predicts survival in pulmonary hypertension. *Am J Respir Crit Care Med* 2006; **174**: 1034-1041
35 **Vachiéry JL**, Coghlan G. Screening for pulmonary arterial hypertension in systemic sclerosis. *Eur Respir Rev* 2009; **18**: 162-169
36 **Mukerjee D**, St George D, Knight C, Davar J, Wells AU, Du Bois RM, Black CM, Coghlan JG. Echocardiography and pulmonary function as screening tests for pulmonary arterial

hypertension in systemic sclerosis. *Rheumatology* (Oxford) 2004; **43**: 461-466
37 **Frea S**, Capriolo M, Marra WG, Cannillo M, Fusaro E, Libertucci D, Morello M, Gaita F. Echo Doppler predictors of pulmonary artery hypertension in patients with systemic sclerosis. *Echocardiography* 2011; **28**: 860-869
38 **Hinchcliff M**, Fischer A, Schiopu E, Steen VD. Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS): baseline characteristics and description of study population. *J Rheumatol* 2011; **38**: 2172-2179
39 **Vonk M**, Coghlan G, Bonderman D, Denton C, Distler O, Grunig E, Khanna D, McLaughlin V, Muller-Ladner U, Pope J, Seibold J. The DETECT study: a two-staged, prospective, observational, cohort study in scleroderma patients to evaluate screening tests and the incidence of pulmonary arterial hypertension and pulmonary hypertension. *Clin Exp Rheumatol* 2010; **28**: Suppl: 55
40 **Hassoun PM**. Therapies for scleroderma-related pulmonary arterial hypertension. *Expert Rev Respir Med* 2009; **3**: 187-196
41 **McLaughlin V**, Humbert M, Coghlan G, Nash P, Steen V. Pulmonary arterial hypertension: the most devastating vascular complication of systemic sclerosis. *Rheumatology* (Oxford) 2009; **48** Suppl 3: iii25-iii31
42 **Badesch DB**, Abman SH, Simonneau G, Rubin LJ, McLaughlin VV. Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines. *Chest* 2007; **131**: 1917-1928
43 **Badesch DB**, Abman SH, Ahearn GS, Barst RJ, McCrory DC, Simonneau G, McLaughlin VV. Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004; **126**: 35S-62S
44 **Humbert M**, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. *N Engl J Med* 2004; **351**: 1425-1436
45 **Gomberg-Maitland M**, Olschewski H. Prostacyclin therapies for the treatment of pulmonary arterial hypertension. *Eur Respir J* 2008; **31**: 891-901
46 **Badesch DB**, Tapson VF, McGoon MD, Brundage BH, Rubin LJ, Wigley FM, Rich S, Barst RJ, Barrett PS, Kral KM, Jöbsis MM, Loyd JE, Murali S, Frost A, Girgis R, Bourge RC, Ralph DD, Elliott CG, Hill NS, Langleben D, Schilz RJ, McLaughlin VV, Robbins IM, Groves BM, Shapiro S, Medsger TA. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. *Ann Intern Med* 2000; **132**: 425-434
47 **Humbert M**, Sanchez O, Fartoukh M, Jagot JL, Le Gall C, Sitbon O, Parent F, Simonneau G. Short-term and long-term epoprostenol (prostacyclin) therapy in pulmonary hypertension secondary to connective tissue diseases: results of a pilot study. *Eur Respir J* 1999; **13**: 1351-1356
48 **Sitbon O**, Humbert M, Nunes H, Parent F, Garcia G, Hervé P, Rainisio M, Simonneau G. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol* 2002; **40**: 780-788
49 **McLaughlin VV**, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation* 2002; **106**: 1477-1482
50 **Kowal-Bielecka O**, Landewé R, Avouac J, Chwiesko S, Miniati I, Czirjak L, Clements P, Denton C, Farge D, Fligelstone K, Földvari I, Furst DE, Müller-Ladner U, Seibold J, Silver RM, Takehara K, Toth BG, Tyndall A, Valentini G, van den Hoogen F, Wigley F, Zulian F, Matucci-Cerinic M. EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). *Ann Rheum Dis* 2009; **68**: 620-628
51 **Simonneau G**, Barst RJ, Galie N, Naeije R, Rich S, Bourge RC, Keogh A, Oudiz R, Frost A, Blackburn SD, Crow JW, Rubin LJ. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2002; **165**: 800-804
52 **Oudiz RJ**, Schilz RJ, Barst RJ, Galié N, Rich S, Rubin LJ, Simonneau G. Treprostinil, a prostacyclin analogue, in pulmonary arterial hypertension associated with connective tissue disease. *Chest* 2004; **126**: 420-427
53 **Olschewski H**, Simonneau G, Galiè N, Higenbottam T, Naeije R, Rubin LJ, Nikkho S, Speich R, Hoeper MM, Behr J, Winkler J, Sitbon O, Popov W, Ghofrani HA, Manes A, Kiely DG, Ewert R, Meyer A, Corris PA, Delcroix M, Gomez-Sanchez M, Siedentop H, Seeger W. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med* 2002; **347**: 322-329
54 **Launay D**, Hachulla E, Hatron PY, Goullard L, Onimus T, Robin S, Fauchais AL, Queyrel V, Michon-Pasturel U, Hebbar M, Saulnier F, Devulder B. Aerosolized iloprost in CREST syndrome related pulmonary hypertension. *J Rheumatol* 2001; **28**: 2252-2256
55 **Dupuis J**, Hoeper MM. Endothelin receptor antagonists in pulmonary arterial hypertension. *Eur Respir J* 2008; **31**: 407-415
56 **Channick RN**, Simonneau G, Sitbon O, Robbins IM, Frost A, Tapson VF, Badesch DB, Roux S, Rainisio M, Bodin F, Rubin LJ. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet* 2001; **358**: 1119-1123
57 **Rubin LJ**, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, Pulido T, Frost A, Roux S, Leconte I, Landzberg M, Simonneau G. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002; **346**: 896-903
58 **Denton CP**, Humbert M, Rubin L, Black CM. Bosentan treatment for pulmonary arterial hypertension related to connective tissue disease: a subgroup analysis of the pivotal clinical trials and their open-label extensions. *Ann Rheum Dis* 2006; **65**: 1336-1340
59 **Denton CP**, Pope JE, Peter HH, Gabrielli A, Boonstra A, van den Hoogen FH, Riemekasten G, De Vita S, Morganti A, Dölberg M, Berkani O, Guillevin L. Long-term effects of bosentan on quality of life, survival, safety and tolerability in pulmonary arterial hypertension related to connective tissue diseases. *Ann Rheum Dis* 2008; **67**: 1222-1228
60 **Girgis RE**, Mathai SC, Krishnan JA, Wigley FM, Hassoun PM. Long-term outcome of bosentan treatment in idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension associated with the scleroderma spectrum of diseases. *J Heart Lung Transplant* 2005; **24**: 1626-1631
61 **McLaughlin VV**. Survival in patients with pulmonary arterial hypertension treated with first-line bosentan. *Eur J Clin Invest* 2006; **36** Suppl 3: 10-15
62 **Williams MH**, Das C, Handler CE, Akram MR, Davar J, Denton CP, Smith CJ, Black CM, Coghlan JG. Systemic sclerosis associated pulmonary hypertension: improved survival in the current era. *Heart* 2006; **92**: 926-932
63 **Barst RJ**. Sitaxsentan: a selective endothelin-A receptor antagonist, for the treatment of pulmonary arterial hypertension. *Expert Opin Pharmacother* 2007; **8**: 95-109
64 **Barst RJ**, Langleben D, Badesch D, Frost A, Lawrence EC, Shapiro S, Naeije R, Galie N. Treatment of pulmonary arterial hypertension with the selective endothelin-A receptor antagonist sitaxsentan. *J Am Coll Cardiol* 2006; **47**: 2049-2056
65 **Langleben D**, Brock T, Dixon R, Barst R. STRIDE 1: effects of the selective ET(A) receptor antagonist, sitaxsentan sodium, in a patient population with pulmonary arterial hypertension that meets traditional inclusion criteria of previous pulmonary arterial hypertension trials. *J Cardiovasc Pharmacol* 2004; **44** Suppl 1: S80-S84
66 **Galié N**, Badesch D, Oudiz R, Simonneau G, McGoon MD, Keogh AM, Frost AE, Zwicke D, Naeije R, Shapiro S, Olschewski H, Rubin LJ. Ambrisentan therapy for pulmonary arterial hypertension. *J Am Coll Cardiol* 2005; **46**: 529-535
67 **Galiè N**, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, Fleming T, Parpia T, Burgess G, Branzi A, Grimminger F, Kurzyna M, Simonneau G. Sildenafil citrate ther-

apy for pulmonary arterial hypertension. *N Engl J Med* 2005; **353**: 2148-2157
68 **Badesch DB**, Hill NS, Burgess G, Rubin LJ, Barst RJ, Galiè N, Simonneau G. Sildenafil for pulmonary arterial hypertension associated with connective tissue disease. *J Rheumatol* 2007; **34**: 2417-2422
69 **Galiè N**, Brundage BH, Ghofrani HA, Oudiz RJ, Simonneau G, Safdar Z, Shapiro S, White RJ, Chan M, Beardsworth A, Frumkin L, Barst RJ. Tadalafil therapy for pulmonary arterial hypertension. *Circulation* 2009; **119**: 2894-2903
70 **O'Callaghan DS**, Gaine SP. Combination therapy and new types of agents for pulmonary arterial hypertension. *Clin Chest Med* 2007; **28**: 169-185, ix
71 **McLaughlin VV**, Oudiz RJ, Frost A, Tapson VF, Murali S, Channick RN, Badesch DB, Barst RJ, Hsu HH, Rubin LJ. Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2006; **174**: 1257-1263
72 **Simonneau G**, Rubin LJ, Galiè N, Barst RJ, Fleming TR, Frost AE, Engel PJ, Kramer MR, Burgess G, Collings L, Cossons N, Sitbon O, Badesch DB. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. *Ann Intern Med* 2008; **149**: 521-530
73 **Mathai SC**, Girgis RE, Fisher MR, Champion HC, Housten-Harris T, Zaiman A, Hassoun PM. Addition of sildenafil to bosentan monotherapy in pulmonary arterial hypertension. *Eur Respir J* 2007; **29**: 469-475
74 **Opitz C**, Klein-Weigel PF, Riemekasten G. Systemic sclerosis - a systematic overview: part 2 - immunosuppression, treatment of SSc-associated vasculopathy, and treatment of pulmonary arterial hypertension. *Vasa* 2011; **40**: 20-30
75 **Mathai SC**, Hassoun PM. Pulmonary arterial hypertension associated with systemic sclerosis. *Expert Rev Respir Med* 2011; **5**: 267-279
76 **Fukumoto Y**, Shimokawa H. Recent progress in the management of pulmonary hypertension. *Circ J* 2011; **75**: 1801-1810
77 **Ghofrani HA**, Seeger W, Grimminger F. Imatinib for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2005; **353**: 1412-1413
78 **Souza R**, Sitbon O, Parent F, Simonneau G, Humbert M. Long term imatinib treatment in pulmonary arterial hypertension. *Thorax* 2006; **61**: 736
79 **ten Freyhaus H**, Dumitrescu D, Bovenschulte H, Erdmann E, Rosenkranz S. Significant improvement of right ventricular function by imatinib mesylate in scleroderma-associated pulmonary arterial hypertension. *Clin Res Cardiol* 2009; **98**: 265-267
80 **Ghofrani HA**, Morrell NW, Hoeper MM, Olschewski H, Peacock AJ, Barst RJ, Shapiro S, Golpon H, Toshner M, Grimminger F, Pascoe S. Imatinib in pulmonary arterial hypertension patients with inadequate response to established therapy. *Am J Respir Crit Care Med* 2010; **182**: 1171-1177
81 **Maurer B**, Busch N, Jüngel A, Pileckyte M, Gay RE, Michel BA, Schett G, Gay S, Distler J, Distler O. Transcription factor fos-related antigen-2 induces progressive peripheral vasculopathy in mice closely resembling human systemic sclerosis. *Circulation* 2009; **120**: 2367-2376
82 **Bull TM**. Screening and therapy of pulmonary hypertension in systemic sclerosis. *Curr Opin Rheumatol* 2007; **19**: 598-603
83 **Schachna L**, Medsger TA, Dauber JH, Wigley FM, Braunstein NA, White B, Steen VD, Conte JV, Yang SC, McCurry KR, Borja MC, Plaskon DE, Orens JB, Gelber AC. Lung transplantation in scleroderma compared with idiopathic pulmonary fibrosis and idiopathic pulmonary arterial hypertension. *Arthritis Rheum* 2006; **54**: 3954-3961

S- Editor Wu X **L- Editor** A **E- Editor** Wu X

World Journal of Rheumatology

Online Submissions: http://www.wjgnet.com/esps/
wjrheumato@wjgnet.com
doi:10.5499/wjr.v2.i2.21

World J Rheumatol 2012 October 3; 2(2): 21-26
ISSN 2220-3214 (online)

BRIEF ARTICLE

Spinal accessory neuropathy in patients with chronic neck pain

Mohamed A Hefny, Mona S Ghaly, Sahar M Greish, Noha M Abogresha, Ayman E Fahim

Mohamed A Hefny, Mona S Ghaly, Department of Rheumatology and Rehabilitation, Faculty of Medicine, Suez Canal University, 4111 Ismailia, Egypt
Sahar M Greish, Noha M Abogresha, Department of Physiology, Faculty of Medicine, Suez Canal University, 4111 Ismailia, Egypt
Ayman E Fahim, Department of Occupational Medicine, Faculty of Medicine, Suez Canal University, 4111 Ismailia, Egypt
Author contributions: Ghaly MS, Hefny MA, Greish SM, Abogresha NM and Fahim AE wrote the paper; Fahim AE performed the statistics and revised the manuscript; Greish SM and Abogresha NM revised the literature and the electrodiagnostic data and helped in editing the manuscript; Ghaly MS and Hefny MA recruited the patients, performed rheumatologic examination and electrodiagnosis, revised statistical data, and helped in submitting the manuscript.
Correspondence to: Mona S Ghaly, MD, Department of Rheumatology and Rehabilitation, Faculty of Medicine, Suez Canal University, 4111 Ismailia, Egypt. xmghaly@gmail.com
Telephone: +20-14-3516507 Fax: +20-64-3230539
Received: July 14, 2012 Revised: August 31, 2012
Accepted: September 6, 2012
Published online: October 3, 2012

Abstract

AIM: To assess the presence of spinal accessory neuropathy in patients with chronic neck pain.

METHODS: Patients with pain either regional or focal in the neck or shoulders for at least 6 mo (chronic neck pain) were recruited randomly from the Rheumatology and Rehabilitation Outpatient Clinic at the Faculty of Medicine-Suez Canal University. Two groups were compared: 30 patients with chronic neck pain with mean age (36.97 ± 12.45 years) and 10 apparently healthy controls. Trapezius muscle examination including inspection and range of motion both active and passive was performed. A full clinical neurological examination was carried out to exclude peripheral neuropathy and motor neuron disease. According to the subject's type of work, cases were categorized into labor-intensive and non-labor intensive tasks. A nerve conduction study (NCS) was performed on spinal accessory nerves at both sides for all patients and controls. Parameters including latencies and amplitudes of compound motor action potential (CMAP) were compared with the chronicity of neck pain using the neck disability score. This cross sectional study was carried in the Rheumatology and Rehabilitation Department, at Suez Canal University Hospital, Ismailia, Egypt.

RESULTS: Physical examination revealed that 80% of cases had spinal trapezius muscle spasm. Restricted neck motion was present in 16.6% of cases. No one suffered from muscle wasting or weakness. Pain was bilateral in 18 patients (60%), localized to the right side in six patients (20%) and localized to the left side in six patients (20%). The causes of neck pain in the patients studied were nonspecific, due to physical stresses, cervical spondylosis and mild cervical disc herniation. Mean disease duration in patients with labor-intensive tasks was (3.9 ± 2.1 years), which was longer than that in patients with non-labor intensive tasks (3.1 ± 1.9 years); however, this difference was statistically insignificant. Spinal accessory NCSs were performed while subjects were in sitting positions and relaxed with naturally suspended arms to minimize muscular movement. The results of electrophysiological studies revealed that mean right and left latencies of the spinal accessory nerve were 2.96 ± 0.69 ms, 2.98 ± 0.61 ms in the patient group and 2.44 ± 0.38 ms, 2.33 ± 0.36 ms in control group respectively. These differences were statistically significant with P = 0.028 and 0.006 respectively. Spinal accessory NCS showed normal CMAP amplitude in both patients and controls. Comparing the results of the neck disability index (NDI) to different characteristics in patients with chronic neck pain, showed that patients with labor-intensive work had a higher NDI score mean (34.7 ± 9.5) compared to those with non-labor-intensive work, with significant statistical difference (P = 0.011). In addition, mean NDI scores were higher in males, and patients aged over 40 years and this difference was statistically sig-

nificant (P = 0.007 and P = 0.009 respectively). Correlation studies between right and left spinal accessory nerve latencies and disability percent calculated using the NDI revealed a positive correlation. Moreover, there was a positive correlation between age and disability percent.

CONCLUSION: This study demonstrates electrophysiological evidence of demyelination in a significant proportion of patients with chronic cervical pain.

Key words: Accessory nerve; Electrophysiology; Chronic neck pain; Neck disability index questionnaire

Peer reviewer: Javier Alberto Cavallasca, MD, Staff Physician, Section of Rheumatology and Autoimmune Diseases, Hospital JB Iturraspe, Boulevard Pellegrini 3551, CP 3000, Santa Fe, Argentina

Hefny MA, Ghaly MS, Greish SM, Abogresha NM, Fahim AE. Spinal accessory neuropathy in patients with chronic neck pain. *World J Rheumatol* 2012; 2(2): 21-26 Available from: URL: http://www.wjgnet.com/2220-3214/full/v2/i2/21.htm DOI: http://dx.doi.org/10.5499/wjr.v2.i2.21

INTRODUCTION

Chronic neck pain is pain that can come from any number of disorders and diseases that may affect almost any tissue, bone, or gland located in the neck. Neck pain is a common problem, with two-thirds of the population having it at some point in their lives[1] and of whom about 19% suffer from chronic neck pain[2].

Typically, neck pain is not caused by anything serious; emotional and physical stresses can create tension in the neck muscles, and chemical stress (tobacco, unhealthy foods, or even medication) can affect muscle tone and the nerves of the neck[3]. Major causes of neck pain include: carotid artery dissection, head and neck cancer, referred pain from acute coronary syndrome, infections as retropharyngeal abscess, spondylosis, spinal canal stenosis and severe spinal disc herniation[4].

When the neck muscles contract, they can apply pressure to the bones of the neck, causing slight deviations in positioning resulting in pain and a stiff neck. If the stress situation continues, the pain persists and becomes chronic[5]. Pain develops in the neck and may spread to the shoulder or base of the skull. Movement of the neck feels restricted[6].

The head is supported by the neck, which is made up of seven vertebrae stacked one on top of the other and cushioned by discs of cartilage. The lower joints in the neck provide the main supportive structure for the head to sit on. Muscles of the neck provide movement and additional support. Thus, when the support system is affected muscles in the area tighten[7].

Anatomically, the trapezius muscle is a large, superficial muscle that is supplied by the spinal accessory nerve and is composed of upper, middle, and lower-functional segments. Physiologically, the trapezius muscle is a major scapular stabilizer and contributes to scapulothoracic rhythm by elevating, rotating and retracting the scapula[8].

To keep the body and head in an erect posture and coordinate the neck and upper-back movements, this muscle always requires sustained contraction. It has been found that trapezius muscle spasm is common with chronic neck pain whatever its cause[9].

Therefore, we hypothesize chronic trapezius spasm associated with chronic neck pain, might result in compression of the spinal accessory nerve, leading to weakness of the trapezius muscle, thus weakening one of the cervical spine support systems and as a result causing neck pain.

Several causes were found to affect the spinal accessory nerve; for instance, nerve injury occurs after a penetrating trauma to the shoulder or surgical dissection in the posterior triangle of the neck[10]. Neuropathy may result in association with Vernet syndrome (i.e., tumor near jugular foramen) poliomyelitis, motor neuron disease, brachial neuritis, syringomyelia, or enlarged posterior cervical lymph nodes near the nerve[11].

Therefore, we aimed to investigate the presence of spinal accessory neuropathy in patients with chronic neck pain.

MATERIALS AND METHODS

Patients

Thirty patients diagnosed with chronic neck pain were included in the study and were referred for neurophysiological evaluation. They included patients of both genders between 17 years and 64 years of age (36.97 ± 12.45 years). A control group of 10 healthy subjects of both sexes and age matched with no prior history of cervical pain were included in the study.

Patients, who had given their permission, were recruited randomly at the Rheumatology and Rehabilitation outpatient clinic from December 2011 through February 2012 by the two senior residents at the Suez Canal University Hospital. Inclusion criterion was pain either regional or focal in the neck or shoulders for at least 6 mo. Patients were excluded if they had history of trauma, surgical procedure in the posterior neck triangle, injections or manipulation in the cervical area; history of diabetes mellitus, motor neuron disease, brachial neuritis and syringomyelia; or swellings (soft tissue or lymph nodes) in the posterior triangle of the neck. Trapezius muscle examination was performed by inspection for muscle status, presence of fasciculation and palpation of the muscle for spasm. To assess range of motion, we observed the patient while tilting and rotating the head, shrugging both shoulders, and abducting both arms. To assess the strength of the trapezius muscle we asked the patient to perform the same range of motion, testing against resistance. Full neurological examination was performed to clinically exclude peripheral neuropathy and motor neuron disease.

Table 1 Electrophysiological results of the study groups (mean ± SD)

	Cases (n = 30)	Control (n = 10)	P value
Latency in millisecond (ms)			
Left	2.98 ± 0.61	2.33 ± 0.36	0.006[1]
Right	2.96 ± 0.69	2.44 ± 0.38	0.028
Amplitude in millivolt (mv)			
Left	3.29 ± 0.39	3.32 ± 0.42	0.924[1]
Right	3.36 ± 0.39	3.38 ± 0.48	0.899[1]

[1]Mann-Whitney U test.

Cases were categorized into stressful work according to tasks that require more manual handling, specific posture, ergonomic stressors, repetitive actions and intensity of labor *vs* the amount of time or money. Otherwise, work tasks were classified as non-stressful. Informed consent was obtained from all patients and controls before the study according to the regulations mandated by the Research Ethics Committee at Suez Canal University.

Methods

Dantec Keypoint® 4 electromyography was used for spinal accessory nerve conduction studies (NCSs). During the NCSs, subjects were seated and relaxed with naturally suspended arms to minimize muscular movement in the test. We then used a bipolar electrode for stimulation, which was performed at the posterior border of the sternocleidomastoid, midway between the mastoid process and the suprasternal notch at the level of the upper margin of the thyroid cartilage.

Surface electrodes were placed using a technique similar to that of Cherington[12], we placed paired electrodes with the active electrode at the midpoint between the acromion of the scapula and the bony prominence of the seventh cervical spinal process and the reference electrode on the acromion. The ground electrode was placed between the stimulation and recording electrodes.

The latency and amplitude of the compound motor action potentials (CMAPs) were measured from baseline to peak and calculated automatically; the results were interpreted according to Kraft[13] (latency, 1.8-3.0 ms, amplitude, 3-4 mv). Skin temperature, measured at the neck by surface temperature-recording label, ranged from 32 ℃ to 34 ℃.

To assess the disability caused by neck pain, we used the neck disability index (NDI) questionnaire. The NDI is a 10-item self-administered questionnaire measuring disability in patients with neck pain. Each item is scored from 0 to 5 for a maximum score of 50; the higher the score, the greater the disability. Disability percent is calculated by multiplying the results by two[14].

Statistical analyses

Student t tests, χ^2, and Mann-Whitney U test were performed for two sample comparisons of neck pain duration, neck pain questionnaire results and NCS findings between patient groups and controls. The analysis of variance test was used for three sample comparisons in the results of NDI between the symptomatic sides and non-symptomatic sides of neck pain patients. Level of significance was set at 0.05. All statistical analyses were performed with SPSS version 19.0 for Windows.

Table 2 Characteristics of subjects studied and neck disability index score

Characteristics	Number of patients	Score of NDI[3]	P value
Work task			
Stressful	22	34.7 ± 9.5	0.011
Non-stressful	8	24.5 ± 3.1	
Handedness			
Right	28	32.2 ± 9.7	0.766
Left	2	34.1 ± 8.7	
Sex			
Male	13	37.5 ± 9.8	0.007
Female	17	28.4 ± 7.4	
Pain site			
Right	6	27.3 ± 9.1	0.197[1]
Left	6	30.1 ± 6.8	
Both	18	34.8 ± 9.8	
Age (yr)			
< 40	18	28.2 ± 6.8	0.009[2]
⩾ 40	12	38.1 ± 9.8	
Disease duration (yr)			
< 3	11	30.1 ± 8.4	0.377
⩾ 3	19	33.4 ± 10.1	

[1]Analysis of variance test; [2]Mann-Whitney U test; [3]mean ± SD. Statistically significant at $P < 0.05$, comparison of patients in the study group. NDI: Neck disability index.

RESULTS

Thirty patients (17 females; 56.7% and 13 males; 43.3%) diagnosed with chronic neck pain were submitted in the study. Mean disease duration in patients with stressful work was 3.9 ± 2.1 years, which was longer than the mean disease duration in patients with non-stressful work (3.1 ± 1.9 years); however this difference was statistically insignificant.

Pain was bilateral in 18 patients (60%), localized to the Right (Rt.) side in 6 patients (20%) and localized to left (Lt.) side also in 6 patients (20%) (Table 1). Muscle spasm was experienced by 24 patients (80%). Restricted neck motion was present in five patients (16.6%). No one suffered from muscle wasting or weakness. The causes of neck pain in the patients studied were nonspecific due to physical stresses (8 patients, 26.7%), cervical spondylosis (17 patients, 56.7%) and mild cervical disc herniation (5 patients, 16.6%).

There was significant difference between cases and controls among means of Rt. and Lt. spinal accessory nerve latencies (P = 0.028, P = 0.006 respectively) with recordings on the upper segments of the trapezius muscles. No significant difference was found in Rt. and Lt. spinal accessory amplitude means between cases and controls (Table 2). Comparing the results of the NDI

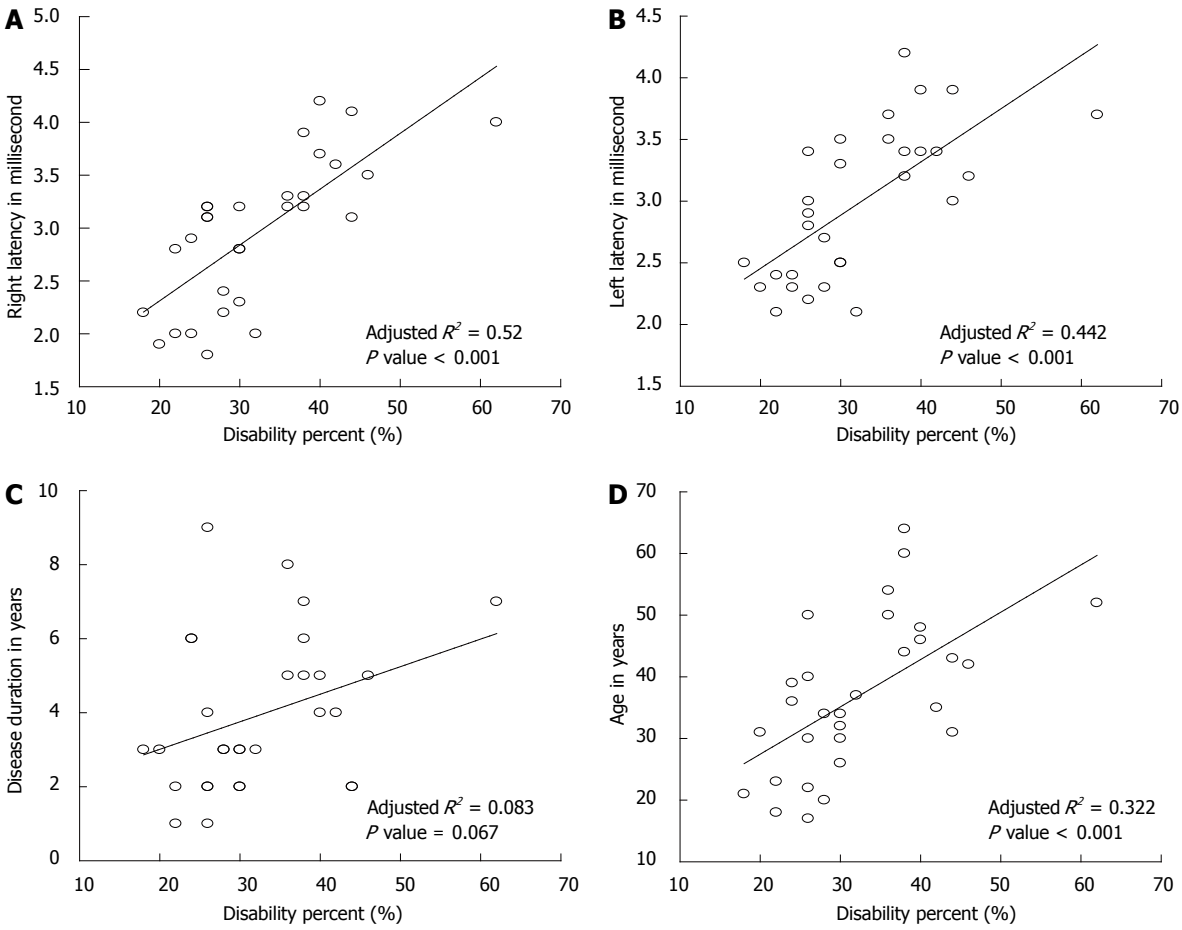

Figure 1 Relation between neck disability index and right latency (A), left latency (B), disease duration (C) and age (D).

to different characteristics in patients with chronic neck pain, we found that there were higher means in males, labor-intensive work and patients aged over 40 years; these differences were statistically significant (Table 2). Figure 1 consist of scatter plots showing positive correlation between Rt. and Lt. latencies and age with disability percent calculated by NDI.

DISCUSSION

Chronic neck pain is pain that occurs over a long period, usually more than six months. There are many causes for this condition[7]. Chronic neck pain is associated with spasm in neck muscles one of which is the trapezius muscle[15].

The trapezius is a large muscle that anatomically consists of three distinct parts: descending, transverse and ascending, which play different but complementary roles in trapezius muscle function[16]. Its main role is related to shoulder movement but it is also essential to keep the head in an erect posture and coordinate neck and back movements by sustained contraction. It is supplied by the spinal accessory nerve[17].

Our study of spinal accessory nerve conduction shows normal values for CMAP amplitude but with prominently prolonged latencies in comparison to the control group.

These results contradicted those of Chang *et al*[9] who searched for spinal accessory nerve neuropathy in myofascial pain syndrome (MFPS) and found that the amplitude of CMAPs of spinal accessory nerves recorded from the upper segments of trapezius muscles were significantly smaller in the symptomatic and asymptomatic sides of MFPS patients than in controls. There were no significant differences regarding latencies and nerve conduction velocities between the symptomatic and asymptomatic sides neither of MFPS nor between cases and controls. They explained these electrophysiological findings by axonal loss or axonal degeneration, which affect a small fraction of nerve and translated clinically as asymptomatic or normal muscle strength, as they found in their MFPS patients. They found that this degeneration may result from fibrosis and taut band associated with MFPS.

Our study found different results as the pathology is different between the two cases. The prolonged latencies in our results indicated that the fastest conductive fibers in the spinal accessory nerve are affected. However, the nerve fibers reacting to stimulation and their supplying muscle fiber are normal. This phenomenon is typical electrophysiologically evident of demyelination. These results confirm our early hypothesis that the spinal accessory nerve may be affected by prolonged neck spasm associated with cases of chronic neck pain.

These findings can be explained as the upper segment of the trapezius muscle is the major portion that is responsible for most of the shoulder and neck movements, and stabilization of the scapula. Certain postures or positions of the shoulder and neck, especially neck spasm, may increase pressure around the spinal accessory nerve. This has been recognized with increased frequency for nerve compression, progressing to demyelination of the nerve, which leads to electrophysiological changes[18].

The exact pathological changes affecting the nerves after prolonged compression have been thoroughly explained in many studies. Early changes consist of edema of the subperineurial space occurring within four hours of compression. Inflammation and fibrin deposits occur from 24-36 h and are followed by proliferation of endoneurial fibroblasts and capillary endothelial cells[19,20]. Demyelination and Schwann cell necrosis appears at seven and ten days of compression[21,22]. Other findings include thinning of the myelin along with evidence of degeneration and regeneration of fibers[23]. Thus the most obvious function disturbance will be related to affection of the myelin sheath that is translated in nerve conduction as prolonged latency.

Measurement of the impact of neck pain on the sufferer presents a challenge due to the variability in pain intensity between patients, and the effect of the disorder on physical and psychological functions[24].

Overall, the literature agrees that the NDI is a valid, reliable, responsive and internally consistent clinical tool to measure self-reported disability as it relates to patients with neck pain[25]. We used the NDI to correlate the disability associated with chronic neck pain and our electrophysiological findings.

Our results revealed that there were strong correlation between Rt. and Lt. spinal accessory latencies and NDI disability percent. These may indicate that spinal neuropathy is associated with further burdens in addition to the primary pathology. This observation is in accordance with the results of Baker[17] (2008), who mentioned that spinal accessory neuropathy causes impaired arm mobility and neck pain.

COMMENTS

Background

Pain located in the neck is a common medical condition. Neck pain can come from a number of disorders and diseases of any tissue in the neck. Examples of common conditions producing neck pain are: degenerative disc disease, neck strain, neck injury such as in whiplash, a herniated disc, or a pinched nerve. The trapezius muscle is a large, superficial muscle that is supplied by the spinal accessory nerve, is a major scapular stabilizer, and contributes to scapulothoracic rhythm by elevating, rotating and retracting the scapula.

Research frontiers

Chronic neck pain is usually first treated by examination to discover the particular reason for an individual's suffering, which can occasionally be difficult. After discovering the reason for a patient's chronic neck pain, it is then treated. To keep the body and head in an erect posture and coordinate the neck and upper-back movements, the trapezius muscle always sustains contraction. It has been found that trapezius muscle spasm is common with chronic neck pain whatever its cause.

Innovations and breakthroughs

In this study, the authors tried to understand the relation between chronic trapezius spasm and chronic neck pain. We hypothesized that chronic neck pain might result in compression of the spinal accessory nerve, leading to trapezius muscle weakness, thus weakening one of the cervical spine support systems and as a result causing neck pain.

Applications

The study results suggest that there is electrophysiological evidence of demyelination of the spinal accessory nerve in a significant proportion of patients with chronic cervical pain.

Terminology

Chronic neck pain is pain that occurs over a long period, usually more than six months. There are many causes for this condition. The pain can range from mild to severe. The spinal accessory nerve is located under the skin on the side of the neck and controls the trapezius muscle, which stabilizes the scapula and shrugs the shoulder.

Peer review

This is a very interesting article which demonstrates the presence of demyelination of the spinal accessory nerve in a significant number of patients with chronic cervical pain. These findings open the discussion about some points such as, the use of certain drugs, mainly those that control neuropathy pain like Pregabalin, and what would be the economic impact of this pathology.

REFERENCES

1 **Binder AI**. Cervical spondylosis and neck pain. *BMJ* 2007; **334**: 527-531
2 **Guez M**, Hildingsson C, Nilsson M, Toolanen G. The prevalence of neck pain: a population-based study from northern Sweden. *Acta Orthop Scand* 2002; **73**: 455-459
3 **Garra G**, Singer AJ, Leno R, Taira BR, Gupta N, Mathaikutty B, Thode HJ. Heat or cold packs for neck and back strain: a randomized controlled trial of efficacy. *Acad Emerg Med* 2010; **17**: 484-489
4 **Mattu A,** Goyal DG. Emergency medicine: avoiding the pitfalls and improving the outcomes. Malden, Massachusetts, USA: Blackwell Publishing, 2007: 47
5 **Vetti N**, Kråkenes J, Eide GE, Rørvik J, Gilhus NE, Espeland A. MRI of the alar and transverse ligaments in whiplash-associated disorders (WAD) grades 1-2: high-signal changes by age, gender, event and time since trauma. *Neuroradiology* 2009; **51**: 227-235
6 **Arana E**, Martí-Bonmatí L, Montijano R, Bautista D, Molla E, Costa S. Relationship between Northwick Park neck pain questionnaire and cervical spine MR imaging findings. *Eur Spine J* 2006; **15**: 1183-1188
7 **Sherman KJ**, Cherkin DC, Hawkes RJ, Miglioretti DL, Deyo RA. Randomized trial of therapeutic massage for chronic neck pain. *Clin J Pain* 2009; **25**: 233-238
8 **Wiater JM**, Bigliani LU. Spinal accessory nerve injury. *Clin Orthop Relat Res* 1999; (368): 5-16
9 **Chang CW**, Chang KY, Chen YR, Kuo PL. Electrophysiologic evidence of spinal accessory neuropathy in patients with cervical myofascial pain syndrome. *Arch Phys Med Rehabil* 2011; **92**: 935-940
10 **Kim DH**, Cho YJ, Tiel RL, Kline DG. Surgical outcomes of 111 spinal accessory nerve injuries. *Neurosurgery* 2003; **53**: 1106-1112; discussion 1106-1112
11 **Dailiana ZH**, Mehdian H, Gilbert A. Surgical anatomy of spinal accessory nerve: is trapezius functional deficit inevitable after division of the nerve? *J Hand Surg Br* 2001; **26**: 137-141
12 **Cherington M**. Accessory nerve. Conduction studies. *Arch Neurol* 1968; **18**: 708-709
13 **Kraft GH**. Axillary, musculocutaneous and suprascapular nerve latency studies. *Arch Phys Med Rehabil* 1972; **53**: 383-387
14 **Vernon H**, Mior S. The Neck Disability Index: a study of reliability and validity. *J Manipulative Physiol Ther* 1991; **14**: 409-415

15 **Gross A**, Miller J, D'Sylva J, Burnie SJ, Goldsmith CH, Graham N, Haines T, Brønfort G, Hoving JL. Manipulation or mobilisation for neck pain. *Cochrane Database Syst Rev* 2010; (1): CD004249
16 **Pu YM**, Tang EY, Yang XD. Trapezius muscle innervation from the spinal accessory nerve and branches of the cervical plexus. *Int J Oral Maxillofac Surg* 2008; **37**: 567-572
17 **Baker SK**. Isolated spinal accessory mononeuropathy associated with neurogenic muscle hypertrophy: restricted neuralgic amyotrophy or stretch-palsy? A case report. *Arch Phys Med Rehabil* 2008; **89**: 559-563
18 **Novak CB**, Mackinnon SE. Nerve injury in repetitive motion disorders. *Clin Orthop Relat Res* 1998; (351): 10-20
19 **Benstead TJ**, Sangalang VE, Dyck PJ. Acute endothelial swelling is induced in endoneurial microvessels by ischemia. *J Neurol Sci* 1990; **99**: 37-49
20 **Cornefjord M**, Sato K, Olmarker K, Rydevik B, Nordborg C. A model for chronic nerve root compression studies. Presentation of a porcine model for controlled, slow-onset compression with analyses of anatomic aspects, compression onset rate, and morphologic and neurophysiologic effects. *Spine* (Phila Pa 1976) 1997; **22**: 946-957
21 **Rempel DM**, Diao E. Entrapment neuropathies: pathophysiology and pathogenesis. *J Electromyogr Kinesiol* 2004; **14**: 71-75
22 **Rempel D**, Dahlin L, Lundborg G. Pathophysiology of nerve compression syndromes: response of peripheral nerves to loading. *J Bone Joint Surg Am* 1999; **81**: 1600-1610
23 **Dahlin LB**, McLean WG. Effects of graded experimental compression on slow and fast axonal transport in rabbit vagus nerve. *J Neurol Sci* 1986; **72**: 19-30
24 **Clair D**, Edmondston S, Allison G. Variability in pain intensity, physical and psychological function in non-acute, non-traumatic neck pain. *Physiother Res Int* 2004; **9**: 43-54
25 **En MC**, Clair DA, Edmondston SJ. Validity of the Neck Disability Index and Neck Pain and Disability Scale for measuring disability associated with chronic, non-traumatic neck pain. *Man Ther* 2009; **14**: 433-438

S- Editor Jiang L **L- Editor** Hughes D **E- Editor** Lu YJ

World Journal of Rheumatology

Online Submissions: http://www.wjgnet.com/esps/
wjrheumato@wjgnet.com
www.wjgnet.com

World J Rheumatol 2012 October 3; 2(2): I
ISSN 2220-3214 (online)

Acknowledgments to reviewers of *World Journal of Rheumatology*

We acknowledge our sincere thanks to our reviewers. Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of our World Series Journals. Both the editors of the journals and authors of the manuscripts submitted to the journals are grateful to the following reviewers for reviewing the articles (either published or rejected) over the past period of time.

Javier Alberto Cavallasca, MD, Staff Physician, Section of Rheumatology and Autoimmune Diseases, Hospital JB Iturraspe, Santa Fe, Argentina, Boulevard Pellegrini 3551, CP 3000, Santa Fe, Argentina

Jörg HW Distler, MD, Department of Internal Medicine 3, University of Erlangen-Nuremberg, Universitätsstr, 29, 91054 Erlangen, Germany

World Journal of Rheumatology

Online Submissions: http://www.wjgnet.com/esps/
wjrheumato@wjgnet.com
www.wjgnet.com

World J Rheumatol 2012 October 3; 2(2): I
ISSN 2220-3214 (online)

Events Calendar 2012

January 16-19, 2012
10th Pan Arab Rheumatology Conference
Jeddah, Saudi Arabia

January 19-21, 2012
World Congress on Debates and Consensus in Bone, Muscle and Joint Diseases
Barcelona, Spain

January 25-28, 2012
Excellence in Rheumatology
Madrid, Spain

February 16-17, 2012
3rd National Conference - Metabolic Bone Disorders 2012
London, United Kingdom

February 24-25, 2012
III Simposio de Enfermedades Sistémicas Autoinmunes
Las Palmas de Gran Canaria, Spain

March 3, 2012
Symposium on Rheumatic Diseases: Hot Topics in Rheumatology (Cedars-Sinai)
California, CA, United States

March 28-31, 2012
Canadian Rheumatology Association Annual Meeting
Victoria, Canada

April 22-29, 2012
OARSI 2012 - World Congress on Osteoarthritis
Barcelona, Spain

May 1-4, 2012
Rheumatology 2012
Glasgow, United Kingdom

May 9-13, 2012
8th International Congress of Autoimmunity 2012
Granada, Spaish

June 6-9, 2012
Annual European Congress of Rheumatology
Berlin, Germany

June 12-15, 2012
EULAR Congress 2012
Madrid, Spain

September 2-5, 2012
34th Scandinavian Congress of Rheumatology
Copenhagen, Denmark

October 5-6, 2012
VII Simposio de Artritis Reumatoide
Bilbao, Spain

November 9-14, 2012
76th Annual Meeting of the American College of Rheumatology
Washington, DC, United States

World Journal of Rheumatology

Online Submissions: http://www.wjgnet.com/esps/
wjrheumato@wjgnet.com
www.wjgnet.com

World J Rheumatol 2012 October 3; 2(2): I-V
ISSN 2220-3214 (online)

GENERAL INFORMATION

World Journal of Rheumatology (*World J Rheumatol*, *WJR*, online ISSN 2220-3214, DOI: 10.5499) is a bimonthly peer-reviewed, online, open-access (OA), journal supported by an editorial board consisting of 116 experts in rheumatology from 29 countries.

The biggest advantage of the OA model is that it provides free, full-text articles in PDF and other formats for experts and the public without registration, which eliminates the obstacle that traditional journals possess and usually delays the speed of the propagation and communication of scientific research results. The open access model has been proven to be a true approach that may achieve the ultimate goal of the journals, i.e. the maximization of the value to the readers, authors and society.

Maximization of personal benefits

The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. So, to realize these desired attributes of *WJR* and create a well-recognized journal, the following four types of personal benefits should be maximized. The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others. (1) Maximization of the benefits of editorial board members: The primary task of editorial board members is to give a peer review of an unpublished scientific article via online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that field at first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution; (2) Maximization of the benefits of authors: Since *WJR* is an open-access journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJR* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading; (3) Maximization of the benefits of readers: Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion; and (4) Maximization of the benefits of employees: It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

Aims and scope

The aim of *WJR* is to report rapidly new theories, methods and techniques for prevention, diagnosis, treatment, rehabilitation and nursing in the field of rheumatology. *WJR* covers topics concerning osteoarthritis, metabolic bone disease, connective tissue diseases, antiphospholipid antibody-associated diseases, spondyloarthropathies, acute inflammatory arthritis, fibromyalgia, polymyalgia rheumatica, vasculitis syndromes, periarticular rheumatic disease, pediatric rheumatic disease, miscellaneous rheumatic diseases, and rheumatology-related therapy, pain management, rehabilitation, traditional medicine, and integrated Chinese and Western medicine. The journal also publishes original articles and reviews that report the results of rheumatology-related applied and basic research in fields such as immunology, physiopathology, cell biology, pharmacology, medical genetics, and pharmacology of Chinese herbs.

Columns

The columns in the issues of *WJR* will include: (1) Editorial: To introduce and comment on the substantial advance and its importance in the fast-developing areas; (2) Frontier: To review the most representative achievements and comment on the current research status in the important fields, and propose directions for the future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (6) Review: To systemically review the most representative progress and unsolved problems in the major scientific disciplines, comment on the current research status, and make suggestions on the future work; (7) Original Articles: To originally report the innovative and valuable findings in rheumatology; (8) Brief Articles: To briefly report the novel and innovative findings in rheumatology; (9) Case Report: To report a rare or typical case; (10) Letters to the Editor: To discuss and make reply to the contributions published in *WJR*, or to introduce and comment on a controversial issue of general interest; (11) Book Reviews: To introduce and comment on quality monographs of rheumatology; and (12) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on the research in rheumatology.

Name of journal

World Journal of Rheumatology

ISSN

ISSN 2220-3214 (online)

Editor-in-chief

Editorial office
World Journal of Rheumatology
Editorial Department: Room 903, Building D,
Ocean International Center,
No. 62 Dongsihuan Zhonglu,
Chaoyang District, Beijing 100025, China
E-mail: wjrheumato@wjgnet.com
http://www.wjgnet.com
Telephone: +86-10-85381892
Fax: +86-10-85381893

Indexed and abstracted in
Digital Object Identifier.

Published by
Baishideng Publishing Group Co., Limited

SPECIAL STATEMENT

All articles published in this journal represent the viewpoints of the authors except where indicated otherwise.

Biostatistical editing
Statistical review is performed after peer review. We invite an expert in Biomedical Statistics to evaluate the statistical method used in the paper, including *t*-test (group or paired comparisons), chi-squared test, Ridit, probit, logit, regression (linear, curvilinear, or stepwise), correlation, analysis of variance, analysis of covariance, *etc*. The reviewing points include: (1) Statistical methods should be described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. Give the number of observations and subjects (*n*). Losses in observations, such as drop-outs from the study should be reported; (4) Values such as ED50, LD50, IC50 should have their 95% confidence limits calculated and compared by weighted probit analysis (Bliss and Finney); and (5) The word 'significantly' should be replaced by its synonyms (if it indicates extent) or the *P* value (if it indicates statistical significance).

Conflict-of-interest statement
In the interests of transparency and to help reviewers assess any potential bias, *WJR* requires authors of all papers to declare any competing commercial, personal, political, intellectual, or religious interests in relation to the submitted work. Referees are also asked to indicate any potential conflict they might have reviewing a particular paper. Before submitting, authors are suggested to read "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Conflicts of Interest" from International Committee of Medical Journal Editors (ICMJE), which is available at: http://www.icmje.org/ethical_4conflicts.html.

Sample wording: [Name of individual] has received fees for serving as a speaker, a consultant and an advisory board member for [names of organizations], and has received research funding from [names of organization]. [Name of individual] is an employee of [name of organization]. [Name of individual] owns stocks and shares in [name of organization]. [Name of individual] owns patent [patent identification and brief description].

Statement of informed consent
Manuscripts should contain a statement to the effect that all human studies have been reviewed by the appropriate ethics committee or it should be stated clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study should be omitted. Authors should also draw attention to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964, as revised in 2004).

Statement of human and animal rights
When reporting the results from experiments, authors should follow the highest standards and the trial should conform to Good Clinical Practice (for example, US Food and Drug Administration Good Clinical Practice in FDA-Regulated Clinical Trials; UK Medicines Research Council Guidelines for Good Clinical Practice in Clinical Trials) and/or the World Medical Association Declaration of Helsinki. Generally, we suggest authors follow the lead investigator's national standard. If doubt exists whether the research was conducted in accordance with the above standards, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study.

Before submitting, authors should make their study approved by the relevant research ethics committee or institutional review board. If human participants were involved, manuscripts must be accompanied by a statement that the experiments were undertaken with the understanding and appropriate informed consent of each. Any personal item or information will not be published without explicit consents from the involved patients. If experimental animals were used, the materials and methods (experimental procedures) section must clearly indicate that appropriate measures were taken to minimize pain or discomfort, and details of animal care should be provided.

SUBMISSION OF MANUSCRIPTS

Manuscripts should be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Number all pages consecutively, and start each of the following sections on a new page: Title Page, Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgements, References, Tables, Figures, and Figure Legends. Neither the editors nor the publisher are responsible for the opinions expressed by contributors. Manuscripts formally accepted for publication become the permanent property of Baishideng Publishing Group Co., Limited, and may not be reproduced by any means, in whole or in part, without the written permission of both the authors and the publisher. We reserve the right to copy-edit and put onto our website accepted manuscripts. Authors should follow the relevant guidelines for the care and use of laboratory animals of their institution or national animal welfare committee. For the sake of transparency in regard to the performance and reporting of clinical trials, we endorse the policy of the ICMJE to refuse to publish papers on clinical trial results if the trial was not recorded in a publicly-accessible registry at its outset. The only register now available, to our knowledge, is http://www.clinicaltrials.gov sponsored by the United States National Library of Medicine and we encourage all potential contributors to register with it. However, in the case that other registers become available you will be duly notified. A letter of recommendation from each author's organization should be provided with the contributed article to ensure the privacy and secrecy of research is protected.

Authors should retain one copy of the text, tables, photographs and illustrations because rejected manuscripts will not be returned to the author(s) and the editors will not be responsible for loss or damage to photographs and illustrations sustained during mailing.

Online submissions
Manuscripts should be submitted through the Online Submission System at: http://www.wjgnet.com/esps/. Authors are highly recommended to consult the ONLINE INSTRUCTIONS TO AUTHORS (http://www.wjgnet.com/2220-3214/g_info_20100722180909.htm) before attempting to submit online. For assistance, authors encountering problems with the Online Submission System may send an email describing the problem to wjrheumato@wjgnet.com, or by telephone: +86-10-85381891. If you submit your manuscript online, do not make a postal contribution. Repeated online submission for the same manuscript is strictly prohibited.

MANUSCRIPT PREPARATION

All contributions should be written in English. All articles must be submitted using word-processing software. All submissions must be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Style should conform to our house format. Required informa-

tion for each of the manuscript sections is as follows:

Title page

Title: Title should be less than 12 words.

Running title: A short running title of less than 6 words should be provided.

Authorship: Authorship credit should be in accordance with the standard proposed by ICMJE, based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

Institution: Author names should be given first, then the complete name of institution, city, province and postcode. For example, Xu-Chen Zhang, Li-Xin Mei, Department of Pathology, Chengde Medical College, Chengde 067000, Hebei Province, China. One author may be represented from two institutions, for example, George Sgourakis, Department of General, Visceral, and Transplantation Surgery, Essen 45122, Germany; George Sgourakis, 2nd Surgical Department, Korgialenio-Benakio Red Cross Hospital, Athens 15451, Greece

Author contributions: The format of this section should be: Author contributions: Wang CL and Liang L contributed equally to this work; Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; and Wang CL, Liang L and Fu JF wrote the paper.

Supportive foundations: The complete name and number of supportive foundations should be provided, e.g. Supported by National Natural Science Foundation of China, No. 30224801

Correspondence to: Only one corresponding address should be provided. Author names should be given first, then author title, affiliation, the complete name of institution, city, postcode, province, country, and email. All the letters in the email should be in lower case. A space interval should be inserted between country name and email address. For example, Montgomery Bissell, MD, Professor of Medicine, Chief, Liver Center, Gastroenterology Division, University of California, Box 0538, San Francisco, CA 94143, United States. montgomery.bissell@ucsf.edu

Telephone and fax: Telephone and fax should consist of +, country number, district number and telephone or fax number, e.g. Telephone: +86-10-85381892 Fax: +86-10-85381893

Peer reviewers: All articles received are subject to peer review. Normally, three experts are invited for each article. Decision for acceptance is made only when at least two experts recommend an article for publication. Reviewers for accepted manuscripts are acknowledged in each manuscript, and reviewers of articles which were not accepted will be acknowledged at the end of each issue. To ensure the quality of the articles published in *WJR*, reviewers of accepted manuscripts will be announced by publishing the name, title/position and institution of the reviewer in the footnote accompanying the printed article. For example, reviewers: Professor Jing-Yuan Fang, Shanghai Institute of Digestive Disease, Shanghai, Affiliated Renji Hospital, Medical Faculty, Shanghai Jiaotong University, Shanghai, China; Professor Xin-Wei Han, Department of Radiology, The First Affiliated Hospital, Zhengzhou University, Zhengzhou, Henan Province, China; and Professor Anren Kuang, Department of Nuclear Medicine, Huaxi Hospital, Sichuan University, Chengdu, Sichuan Province, China.

Abstract

There are unstructured abstracts (no less than 256 words) and structured abstracts (no less than 480). The specific requirements for structured abstracts are as follows:

An informative, structured abstracts of no less than 480 words should accompany each manuscript. Abstracts for original contributions should be structured into the following sections. AIM (no more than 20 words): Only the purpose should be included. Please write the aim as the form of "To investigate/study/…; MATERIALS AND METHODS (no less than 140 words); RESULTS (no less than 294 words): You should present *P* values where appropriate and must provide relevant data to illustrate how they were obtained, e.g. 6.92 ± 3.86 *vs* 3.61 ± 1.67, $P < 0.001$; CONCLUSION (no more than 26 words).

Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

Text

For articles of these sections, original articles and brief articles, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both. The main text format of these sections, editorial, topic highlight, case report, letters to the editors, can be found at: http://www.wjgnet.com/2220-3214/g_info_list.htm.

Illustrations

Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Figures should be either Photoshop or Illustrator files (in tiff, eps, jpeg formats) at high-resolution. Examples can be found at: http://www.wjgnet.com/1007-9327/13/4520.pdf; http://www.wjgnet.com/1007-9327/13/4554.pdf; http://www.wjgnet.com/1007-9327/13/4891.pdf; http://www.wjgnet.com/1007-9327/13/4986.pdf; http://www.wjgnet.com/1007-9327/13/4498.pdf. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: …*etc.* It is our principle to publish high resolution-figures for the printed and E-versions.

Tables

Three-line tables should be numbered 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each table. Detailed legends should not be included under tables, but rather added into the text where applicable. The information should complement, but not duplicate the text. Use one horizontal line under the title, a second under column heads, and a third below the Table, above any footnotes. Vertical and italic lines should be omitted.

Notes in tables and illustrations

Data that are not statistically significant should not be noted. $^{a}P < 0.05$, $^{b}P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of *P* values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used. A third series of *P* values can be expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Other notes in tables or under illustrations should be expressed as ^{1}F, ^{2}F, ^{3}F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc.*, in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

REFERENCES

Coding system

The author should number the references in Arabic numerals according to the citation order in the text. Put reference numbers in square brackets in superscript at the end of citation content or after the cited author's name. For citation content which is part of the narration, the coding number and square brackets should be typeset normally. For example, "Crohn's disease (CD) is associated with increased intestinal permeability[1,2]". If references are cited directly in the text, they should be put together within the text, for example, "From references[19,22-24], we know that..."

When the authors write the references, please ensure that the order in text is the same as in the references section, and also ensure the spelling accuracy of the first author's name. Do not list the same citation twice.

PMID and DOI

Pleased provide PubMed citation numbers to the reference list, e.g. PMID and DOI, which can be found at http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed and http://www.crossref.org/SimpleTextQuery/, respectively. The numbers will be used in E-version of this journal.

Style for journal references

Authors: the name of the first author should be typed in bold-faced letters. The family name of all authors should be typed with the initial letter capitalized, followed by their abbreviated first and middle initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR). The title of the cited article and italicized journal title (journal title should be in its abbreviated form as shown in PubMed), publication date, volume number (in black), start page, and end page [PMID: 11819634 DOI: 10.3748/wjg.13.5396].

Style for book references

Authors: the name of the first author should be typed in bold-faced letters. The surname of all authors should be typed with the initial letter capitalized, followed by their abbreviated middle and first initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR) Book title. Publication number. Publication place: Publication press, Year: start page and end page.

Format

Journals

English journal article (list all authors and include the PMID where applicable)

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/2220-3214/g_info_20100725073806.htm.

Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

Examples for paper writing

Editorial: http://www.wjgnet.com/2220-3214/g_info_20100725071851.htm

Frontier: http://www.wjgnet.com/2220-3214/g_info_20100725071932.htm

Topic highlight: http://www.wjgnet.com/2220-3214/g_info_20100725072121.htm

Observation: http://www.wjgnet.com/2220-3214/g_info_20100725072232.htm

Guidelines for basic research: http://www.wjgnet.com/2220-3214/g_info_20100725072344.htm

Guidelines for clinical practice: http://www.wjgnet.com/2220-3214/g_info_20100725072543.htm

Review: http://www.wjgnet.com/2220-3214/g_info_20100725072656.htm

Original articles: http://www.wjgnet.com/2220-3214/g_info_20100725072755.htm

Brief articles: http://www.wjgnet.com/2220-3214/g_info_20100725072920.htm

Case report: http://www.wjgnet.com/2220-3214/g_info_20100725073015.htm

Letters to the editor: http://www.wjgnet.com/2220-3214/g_info_20100725073136.htm

Book reviews: http://www.wjgnet.com/2220-3214/g_info_20100725073214.htm

Guidelines: http://www.wjgnet.com/2220-3214/g_info_20100725073300.htm

SUBMISSION OF THE REVISED MANUSCRIPTS AFTER ACCEPTED

PAuthors must revise their manuscript carefully according to the revision policies of Baishideng Publishing Group Co., Limited The revised version, along with the signed copyright transfer agreement, responses to the reviewers, and English language Grade B certificate (for non-native speakers of English), should be submitted to the online system via the link contained in the e-mail sent by the editor. If you have any questions about the revision, please send e-mail to esps@wjgnet.com.

Language evaluation

The language of a manuscript will be graded before it is sent for revision. (1) Grade A: priority publishing; (2) Grade B: minor language polishing; (3) Grade C: a great deal of language polishing needed; and (4) Grade D: rejected. Revised articles should reach Grade A or B.

Copyright assignment form

Please download a Copyright assignment form from http://www.wjgnet.com/2220-3214/g_info_20100725073726.htm.

Responses to reviewers

Please revise your article according to the comments/suggestions provided by the reviewers. The format for responses to the reviewers' comments can be found at: http://www.wjgnet.com/2220-3214/g_info_20100725073445.htm.

Proof of financial support

For paper supported by a foundation, authors should provide a copy of the document and serial number of the foundation.

Links to documents related to the manuscript

WJR will be initiating a platform to promote dynamic interactions between the editors, peer reviewers, readers and authors. After a manuscript is published online, links to the PDF version of the submitted manuscript, the peer-reviewers' report and the revised manuscript will be put on-line. Readers can make comments on the peer reviewer's report, authors' responses to peer reviewers, and the revised manuscript. We hope that authors will benefit from this feedback and be able to revise the manuscript accordingly in a timely manner.

Science news releases

Authors of accepted manuscripts are suggested to write a science news item to promote their articles. The news will be released rapidly at EurekAlert/AAAS (http://www.eurekalert.org). The title for news items should be less than 90 characters; the summary should be less than 75 words; and main body less than 500 words. Science news items should be lawful, ethical, and strictly based on your original content with an attractive title and interesting pictures.

Publication fee

WJR is an international, peer-reviewed, Open-Access, online journal. Articles published by this journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license. Authors of accepted articles must pay a publication fee. The related standards are as follows. Publication fee: 600 USD per article. Editorial, topic highlights, book reviews and letters to the editor are published free of charge.