Interstitial Cystitis — Cystoscopy, Hydrodistention, Potassium Test, Urodynamics, Pathology — What is the value of each?

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ABSTRACT

Interstitial cystitis (IC) is characterized by bladder pain associated with urgency, frequency, nocturia, dysuria and sterile urine. The diagnosis of this disease remains unclear and should be based on exclusion of other diseases. Cystoscopy can be performed to exclude bladder cancer or chronic granulomatous cystitis. Hydrodistention under general anesthesia is the classical diagnostic test to demonstrate glomerulation and mucosal fissure in IC, and can be used to classify the severity of disease as well as the chance of recovery after medical treatment. A potassium chloride test provides a diagnosis of urothelial leak and measurement of therapeutic effect of surface protective treatment. An urodynamic study can differentiate detrusor overactivity from sensory urgency in IC. Low bladder compliance also predicts a poor therapeutic outcome of IC. Pathological examination can diagnose bladder cancer and granulomatous disease of the bladder. Although none of these, even together, is able to diagnose IC adequately, they can provide valuable information on this mysterious disease. *Key words:* interstitial cystitis, cystoscopy, urodynamics, pathology, hydrodistention, potassium test

INTRODUCTION

Interstitial cystitis (IC) is a syndrome of mystery in urology. IC is characterized by bladder pain associated with urgency, frequency, nocturia, dysuria and sterile urine. The diagnosis of IC is based on the symptomatology and urological findings including characteristic cystoscopic features after hydrodistention under anesthesia [1]. Although this disease has been known for more than a century [2], the diagnosis of IC remains unclear and is based on exclusion of other diseases.

IC has been classified into the classic IC and non-ulcer types IC based on cystoscopic findings. Classic IC, also called Hunner's ulcer, is found in 5% to 20% of IC patients and is characterized by observable bladder ulcerations after hydrodistention [3]. Non-ulcer IC, also called early IC, is characterized by glomerulation and petechia formation after hydrodistention under anesthesia. Although many pathogeneses of IC have been proposed, the actual etiology remains unclear [4]. Possible etiologies of IC include: (1) a post-infection autoimmune process, (2) mast cell activation induced by inflammation, toxins or stress, (3) urothelial dysfunction and increased permeability of the urothelium and (4) neurogenic inflammation resulting in serial reactions including potassium ion (K) diffusion, mast cell activation, up-regulation of sensory fibers, release of neuropeptide (substance P), and bladder pain. As the pathogenesis of IC remains unclear, therefore the current diagnostic tests for IC are largely based on discovery of these underlying pathophysiologies.

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Cystoscopy

Since IC is a diagnosis of exclusion, it is rational to exclude any possible etiology for the presenting symptoms of bladder pain, frequency and urgency. Urinalysis is the fundamental test for exclusion of urinary tract infection. A KUB film is necessary to exclude the possibility of a lower ureteral stone that may cause bladder irritative symptoms. Cystoscopy, in some patients suspicious of IC, should also be performed in order to exclude bladder malignancy, possible bladder outlet obstruction and other pathologies such as granulomatous inflammation or a foreign body in the bladder wall especially when the patient has previously undergone a hysterectomy.

Patients with IC-like symptoms may have microscopic hematuria. The prevalence of benign microscopic hematuria was 24% in a cohort of 100 women [5]. When microscopic hematuria are found in men with IC symptoms, carcinoma *in situ* (CIS) of the urinary bladder should be carefully investigated. In my personal experience, CIS was diagnosed in 3 out of 20 men who had previously been diagnosed as IC and their urinalysis at diagnosis showed microscopic hematuria. Random bladder biopsy is necessary whenever cystoscopy or cystoscopic hydrodistention is performed for diagnosis of IC in order to make a differential diagnosis of CIS.

Although cystoscopy is important in detecting CIS, it is not recommended that is performed on every patient with IC-like symptoms. Cystoscopy under local anesthesia is extremely painful in patients with IC; therefore, hydrodistention without general anesthesia is not feasible. We recommend that cystoscopy should be performed in patients with IC-like symptoms and where urinalysis shows microscopic hematuria or where there has been previous hysterectomy or other lower abdominal surgery.

Bladder hydrodistention

Bladder hydrodistention is a recommended test in diagnosis of IC in the NIDDK Diagnosis of IC. In fact, bladder hydrodistention is both a diagnostic and a therapeutic procedure; it is currently the most widely used diagnostic test and treatment procedure for IC [1]. Bladder hydrodistention should be performed under general anesthesia with an intravesical pressure of up to 80 cm water for more than 1 minute. The bladder wall should be carefully inspected for any lesion or fissure. Usually the bladder vasculature will decrease when the intravesical pressure is elevated and bladder mucosa looks pale (Fig. 1A). When the intravesical pressure reaches the desired pressure, hydrodistention

can be kept up for 3 to 5 minutes and then the infused saline is released. Characteristic glomerulation, petechia, splotch hemorrhage and ulceration may appear sequentially during bladder deflation (Fig. 1B). At the end of bladder deflation, diffused hemorrhage or mucosal fissure will occur and the cystoscopic field becomes obscured (Fig. 1C). The purpose of any secondary hydrodistention is to inspect for the presence of mucosal fissures, of ulceration and to estimate the severity of any hemorrhage. Secondary hydrodistention should be performed carefully because inadvertent bladder rupture might occur during this hydrodistention.

IC has previously been classified as classical and early IC. Classical IC is a contracted bladder with presence of Hunner's ulcer patch, whereas early IC shows glomerulation, petechial hemorrhage and mucosal fissure after bladder hydrodistention. Recent investigation has suggested that classical IC (ulceration) may be misleading, because the symptoms may be due to mucosal fissure and severe hemorrhage; chronic IC may be a more accurate description of bladder pathology in patients with a maximum bladder capacity of less than 350 mL.

Bladder hydrodistention can determine the maximal bladder capacity and severity of mucosal hemorrhage in IC patients. Maximal bladder capacity is of predictive value for IC treatment. However, the severity of the cystoscopic findings during hydrodistention does not correlate with the degree of histological inflammation [6]. The severity of glomerulation after cystoscopic hydrodistention has not been demonstrated to be related to the severity of the clinical symptoms, improvement after medical treatment or the maximal bladder capacity. However, in clinical practice, glomerulation after cystoscopic hydrodistention shows a trend involving a decrease in severity after treatment with oral pentosan polysulphate (PPS) or botulinum toxin A injection.

According to the NIDDK criteria for IC, a diagnosis of IC needs at least have two of the following positive factors: (1) pain on bladder filling relieved by emptying, (2) pain (suprapubic, pelvic, urethral, vaginal or perineal), (3) glomerulation on endoscopy after bladder distention by 80 cm water x 1 min and (4) decreased compliance on cystometry [7]. However, the NIDDK criteria would seem to misdiagnose more than 60% of patients with definite or IC-like syndrome [8]. Nevertheless, bladder hydrodistention remains the most popular diagnostic test for IC currently.

For intravesical treatment of IC, hydrodistention of the bladder is the first choice for diagnosis, biopsy and treatment. Although hydrodistention is effective for the relief of the bladder symptoms of IC, the symptoms usually recur within 2 weeks and repeat hydrodistention is necessary. There is no evidence that prolonged hydrodistention has better clinical outcome than a short hydrodistention time (1 minute as recommended by the NIDDK). Prolonged hydrodistention under epidural anesthesia with an intravesical pressure equal to the mean arterial pressure of the patient has been shown to provide long-term benefits. Glemain et al treated 65 consecutive IC patients and found that this treatment was effective in 60% of patients at 6 months and 43.3% at 1 year [9]. However, prolonged hydrodistention might result in bladder necrosis, which may then require cystectomy or bladder substitution [10]. Yamada et al also had similar therapeutic results. In their study, adjuvant hydrodistention under epidural anesthesia was effective for 70% of patients for more than 3 months [11]. Rose et al found that hydrodistention with electromotive drug administration (EMDA) in the doctor's office setting was as effective as hydrodistention of the bladder in the operating room [12].

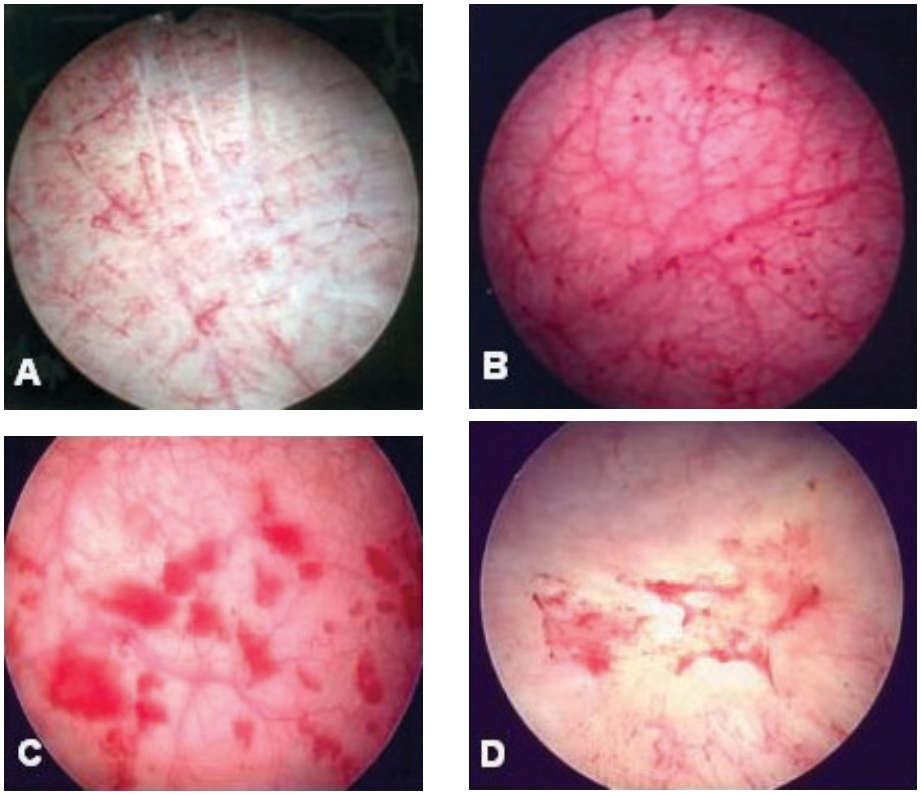

Fig. 1. The characteristic findings after cystoscopic hydrodistention in patients with interstitial cystitis. (A) Decreased vasculature occurs when the intravesical pressure is increased, (B) Characteristic glomerulation develops on bladder deflation, (C) There is mucosal fissure, and splotch hemorrhage (D).

Urodynamic study

A urodynamic study is not an essential test for the diagnosis of IC. However, a urodynamic study remains important for: (1) the exclusion of detrusor overactivity and bladder outlet obstruction (BOO), (2) confirmation of the clinical symptoms of IC, (3) obtaining objective findings of hypersensitivity, (4) determining bladder compliance, (5) assessment of severity of bladder pathology, (6) performing a KCl test after the urodynamic study, and (7) providing objective data when assessing the treatment outcome.

Although urodynamic findings are not diagnostic for IC, most IC bladders have the following characteristics: (1) increased bladder sensation; patients cannot tolerate a

bladder volume of greater than 250 mL, (2) intolerance to increments of bladder volume although compliance is not poor and (3) decrease in bladder compliance. In the author's previous study, a bladder compliance of <30 mL/cm water was found in 16 out of 30 cystoscopic hydrodistention proven IC patients compared with 3 out of 17 patients with painful bladder syndrome without cystoscopic IC findings ($p<0.025$). These IC patients also have a smaller maximal bladder capacity under anesthesia (548 v 612 mL, $p<0.05$) [13]. Patients with early IC tend to have a normal compliance but the compliance decreases in chronic IC. Therefore, bladder compliance may be used as an indicator for prognosis and therapeutic results.

Most IC patients present with an abnormal flow pattern with or without a low maximal flow rate, but this feature also can be found in non-IC patients. Patients with IC usually have a normal flow pattern or an intermittent flow pattern, however, the flow pattern is not likely to be an obstructive type.

In a comparison of the pressure flow results in 100 patients with IC and 40 with frequency urgency syndrome, it was revealed that there was a lower maximum flow rate and higher Pdet in IC patients compared with normal subjects (Pdet <20 cm water, Qmax >15 mL/s). Clinical observation has also found that IC patients have a low flow rate and difficulty in initiating urination (Fig. 2). IC patients often complain of dysuria and straining to void. These observations reveal a possible pathophysiology of IC whereby increased excitability of sensory nerves in the bladder wall might result in increased activity of the pelvic floor muscles; based on this, therefore, biofeedback pelvic floor muscle training (PFMT) might effectively improve IC symptoms.

Although the criteria of IC defined by NIDDK in 1987 declared that the demonstration of phasic involuntary bladder contraction on cystometry may exclude IC, patients with detrusor overactivity and a positive KCl test may also have characteristic IC cystoscopic findings. Intravesical heparin therapy can eliminate detrusor overactivity and IC symptoms in patients who have characteristic cystoscopic IC findings [13]. A high prevalence of IC has been found in women with detrusor overactivity that does not respond to antimuscarinics [14].

A urodynamic study may also be useful in selecting the therapeutic modalities for IC. Antimuscarinic agents can be tried for patients with urodynamic DO after a positive KCl test. Intravesical heparin, PPS or hyaluronic acid therapy can be used as a surface protective treatment for patients with a positive KCl test. Alpha-adrenergic blockers and skeletal muscle relaxant might be effective for IC patients with poorly relaxed pelvic floor muscles.

A urodynamic study can also be used to assess of treatment outcome in patients with IC. Forty women with clinical IC were enrolled in a previous study. Patients underwent a videourodynamic study with the potassium chloride (KCl) test. All patients with a positive KCl test were treated with intravesical heparin 25,000 units twice a week for 3 months. Twenty-nine patients showed a symptom score improvement of more than 50%, and eight had a symptom score improvement of less than 50% but improved nocturia. A urodynamic study at the end of treatment revealed significant improvements in the first sensation of filling (146 ± 55.4 v 96±46.4 mL, $p=0.001$) and cystometric capacity (304 ± 84.8 v 262 ± 89.8 mL, $p=0.002$) [15].

When the above are taken together, although a urodynamic study is not a diagnostic tool for IC, urodynamics can provide useful information for the inclusion and exclusion of IC. Furthermore, treatment based on urodynamic findings can be helpful for IC patients, and a urodynamic study can provide an objective finding for follow-up of therapeutic effects, especially in terms of maximal tolerable bladder capacity and improvement in bladder sensation.

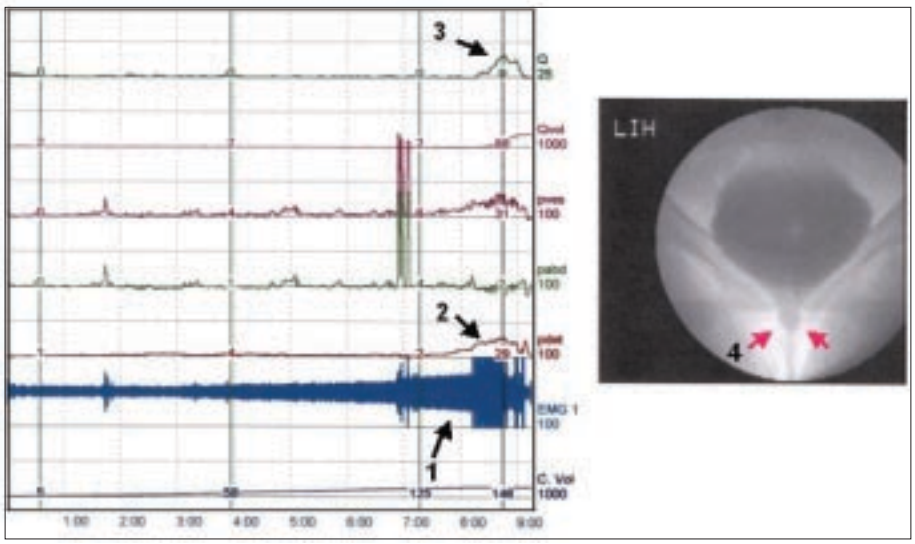

Fig. 2. Videourodynamic findings in a woman with confirmed interstitial cystitis. Poor relaxation of the pelvic floor and urethral sphincter results in increased electromyographic activities (arrow 1), delayed increased detrusor pressure (arrow 2), a low maximum flow rate (arrow 3), and a narrowing of the urethral sphincter during voiding (arrow 4).

Potassium chloride sensitivity test

Glycosaminoglycan (GAG) is a part of the normal bladder epithelium and protects the bladder mucosa from bacterial adhesion and penetration by the toxic substances in the urine [5]. A subset of patients with frequency urgency syndrome has a leaky epithelium and cations (K) can diffuse subepithelially and provoke urgency frequency. Intravesical potassium chloride (KCl, 0.4 M) provoked symptoms in 4% of normal subjects, 75% of patients with IC, 25% of patients with DO, 79% of patients with protamine treated bladder, 42% of patients with heparin treated IC and 100% of patients with irradiation cystitis [16]. Cystometry performed by 0.3 M KCl solution produced a significant reduction in mean cystometric bladder capacity compared to that in normal saline cystometry [17]. Intravesical KCl (40 mL of 0.4 M) can elicit abnormal epithelial permeability responses in the diseased bladder [18]. A positive KCl test was found in 66% of IC patients whereas only 46% of patients with a negative KCl test had IC [19]. All the above evidence suggests that a high concentration KCl solution may be used as medium to test for a defective urothelium, especially in IC bladders. However, the KCl

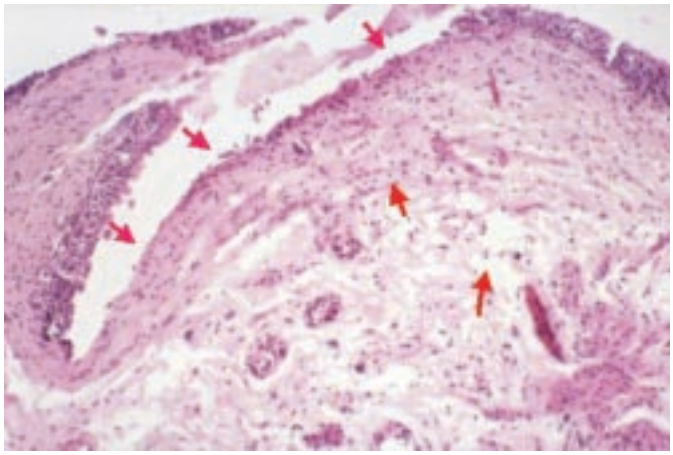

Fig. 3. Histological findings for non-ulcerative interstitial cystitis (early IC). The findings include a denuded mucosa, submucosal inflammation and edema (arrows).

sensitivity test has been found not to correlate with bladder capacity or cystoscopic findings [20]. Patients with bladder pain and a positive KCl test had a 45.2% change of suffering from classic IC [21]. Interestingly, 77% of men with prostatitis also had a positive KCl test [22].

Intravesical sulfated polysaccharide can restore an injured urothelium to normal. A total of 67% of patients with urgency frequency and a positive KCl test show improvement in symptoms and increase in cystometric bladder capacity after heparin therapy [13]. Intravesical hyaluronic acid instillation can improve bladder pain symptoms in 74% of IC patients with a positive KCl test [23].

Pathology

According to previous investigations of bladder pathology in IC, classical IC presents with mucosal ulceration with granulation tissue, marked mononuclear cell infiltration, increased mast cells in the lamina propria and detrusor, the presence of intraurothelial mast cells, perineural inflammatory cells and significant fibrosis. The pathological findings in early IC include mucosal rupture, suburothelial hemorrhage, scanty inflammation and mild submucosal edema. Activation of mast cells is significant in IC bladders. Bladder mastocytosis has been documented in patients with IC. Mast cells are 6 to 8 fold higher in the detrusor compared with controls in classic IC, and 2 to 3 fold higher in non-ulcerative IC. An increase in mucosal mast cells is present in nonulcerative IC [24].

Although the cystoscopic findings after hydrodistention are characteristic in IC patients, pathological findings obtained from IC bladders are not usually diagnostic. Cystoscopic pathology findings in 204 ICDB women were not associated with primary IC symptoms. Among the pathological findings four pathology features were significantly associated with nocturia and frequency: (1) the mast cell count in the lamina propria, (2) complete loss of urothelium, (3) granulation tissue in the lamina propria and (4) vascular density in the lamina propria. A denuded mucosa and submucosal hemorrhage were associated with pain [25].

Several important reports of molecular pathological findings in IC have documented the role of neuroimmunological changes in IC. Neural upregulation occurs both peripherally and centrally in chronic IC [26]. ATP released after bladder distention activates $P2X_3$ receptors, which mediate increases bladder sensation. Fos-protein expression increased in spinal cord neurons in a cyclophosphamide induced cystitis model [27]. A novel protein termed the antiproliferative factor (APF) was found to be uniquely expressed by IC bladder urothelial cells. APF induces increased permeability of normal urothelium grown in culture. Furthermore, APF regulates expression of other cytokines, including upregulating heparin-binding epidermal growth factor-like growth factor and downregulating epidermal growth factor (EGF) in bladder urothelial cells. These cytokine abnormalities were also related to increases in purinergic (ATP) signaling, which could mediate increased bladder sensation [28]. Recent studies of uroplakins, which are specialized proteins expressed only in the apical urothelial cells, also suggest that uroplakins may play a role in the barrier function of the bladder urothelium. Alterations in uroplakins may result in bladder symptoms related to increased permeability or decreased protective function [29]. A large number of urine alterations have been reported and a few are being pursued further by correlating them with bladder biopsy findings or treatment responses. Markers that correlate with specific bladder biopsy features include 1, 4-methylimidazole acetic acid and eosinophil cationic protein (ECP), which correlates with mast cell density, and interleukin (IL)-6, which correlates with mononuclear inflammation. Markers that changed after treatment were as follows: (1) nitric oxide synthase and cyclic guanosine monophosphate increased with oral L-arginine; (2) ECP decreased with subcutaneous heparin; (3) prostaglandin E(2) and kallikrein decreased after bladder distention; (4) neutrophil chemotactic activity decreased after dimethyl sulfoxide; (5) IL-2 inhibitor decreased after oral nifedipine; (6) IL-2, IL-6, and IL-8 decreased after Bacille Calmette-Guerin (BCG) vaccine; and (7) APF and heparin-binding epidermal growth factor changed to or toward normal levels after bladder distention or sacral nerve stimulation [30]. These urine markers may be useful for the detection of interstitial cystitis at an early stage and if this is true then treatment of IC earlier and the use of these markers for assessing treatment outcome may be possible.

Thus, cystoscopy, hydrodistention, the potassium sensitivity test, urodynamics, and pathology each has its role in the diagnosis of IC. However, none can be used solely in the diagnosis or to assess the therapeutic outcome of IC. Currently, diagnosis of IC is still based on the cardinal symptoms of frequency urgency and bladder pain. Evidence based medicine does not require the use of cystoscopy or urodynamics in an IC workup. Cystoscopic hydrodistention provides a way to diagnose classical IC. A urodynamic study, the KCl sensitivity test and pathology provide more information on the disease and may predict therapeutic outcome for IC. Treatment of IC aimed at bladder mucosa dysfunction and chronic inflammation should be given as soon as possible when a patient is suspected of having IC.

Recommended tests for IC

When diagnosing IC, the presenting symptoms are of the utmost important. Unless microscopic hematuria are present, cystoscopy without anesthesia is not necessary for the diagnosis of IC. Patients may be treated at first with antimuscarinics and a non-steroid anti-inflammatory agent for 2 weeks and a 3-day voiding diary should be requested to record their voiding status. If the bladder pain and frequency urgency symptoms persist, a urodynamic study with a KCl test may be advised to exclude the possibility of detrusor overactivity, bladder out-

let obstruction or a neurogenic bladder. In patients with an increased bladder sensation, reduced bladder capacity and a positive KCl test treatment, treatment targeting urothelial dysfunction may be instituted. In Taiwan, because of the regulationsof the Central Health Insurance Bureau, a cystoscopic hydrodistention under general anesthesia is required before treatment with PPS or hyaluronic acid. A bladder biopsy is an optional procedure when carrying out cystoscopic hydrodistention. The pathological results may not diagnostic for IC but can be used to exclude carcinoma *in situ* or granulomatous inflammation of the bladder.

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