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Nitric Oxide in the Painful Bladder/Interstitial Cystitis

L. Renström Koskela, N. P. Wiklund

Die Interstitielle Zystitis (IC) ist eine Entzündungserkrankung der Harnblase unbekannter Ätiologie. Stickoxid (NO) ist ein brauchbares Gas zur Feststellung einer Entzündung in Hohlorganen wie der Harnblase. Bei Patienten mit IC ist der Spiegel endogen gebildeter NO in der Blase im Vergleich zu Patienten ohne Blasenentzündung signifikant erhöht. Es ist noch immer nicht bekannt, ob hohe NO-Werte ein Teil der Pathophysiologie der Krankheit sind und ob diese eine schädigende oder eine schützende Rolle spielen. Die Messung von NO in der Harnblase ist ein nützliches Mittel zur Feststellung einer Entzündung. Damit läßt sich zwischen einer Interstitiellen Zystitis und schmerzhaften Blasensymptomen anderer Ätiologie unterscheiden. Sie kann zudem für die objektive Evaluierung unterschiedlicher Behandlungen eingesetzt werden.

Interstitial cystitis (IC) is an inflammatory disease of the urinary bladder of unknown etiology. Nitric oxide (NO) is a useful gas in detecting inflammation in hollow organs such as the urinary bladder. In patients with IC the levels of endogenously formed NO in the bladder are significantly increased compared to patients without inflammation of the bladder. It still remains unknown whether high levels of NO is a part of the pathophysiology of this disease and whether it has a damaging or protective role. Measuring NO in the urinary bladder is a useful tool in detecting inflammation, thus making it possible to discriminate between interstitial cystitis and painful bladder symptoms of other etiology. It can also be used in the objective evaluation of different treatments. ***J Urol Urogynäkol 2007; 14 (1): 18–19.***

Interstitial Cystitis

Patients with painful bladder symptoms in combination with other lower urinary tract symptoms, such as frequency, urgency and nocturia, are commonly referred to the urologists. These symptoms can be caused by several different diseases affecting the bladder such as bacterial cystitis, bladder outlet obstruction, malignancy, neurological disorders and interstitial cystitis (IC). IC is a chronic inflammatory disease of the urinary bladder and, though, it was described for more than 100 years ago, the etiology and pathogenesis of this disease is yet to be elucidated. Damage to the protective glycosaminoglycan layer in the bladder [1] and immunological processes have been suggested [2, 3].

The diagnosis is based on clinical evaluation, different symptom scores and cystoscopy with bladder distension and biopsies. There are no pathognomonic findings upon cystoscopy but a classical ulcer of Hunner [4] and punctuate petecial hemorrhages observed after hydrodistension [5] suggest the diagnosis of IC. The histopathological features of IC include ulcerations of the mucosa, denuded urothelium, edema and an increase in mast cells and other inflammatory cells. Biopsies though, are mainly performed to rule out carcinoma in situ of the bladder. IC has been poorly defined and epidemiological and clinical studies have often been difficult to compare due to differences in the definition of IC. Moreover, IC can be divided into 2 subgroups that may present differently regarding both clinical and histopathological findings [6, 7]; classic or ulcerous IC and non-ulcerous IC [8, 9]. In 1988, the National Institute of Arthritis, Diabetes, Digestive and Kidney Disease (NIDDK) [10] developed criteria for IC to facilitate research and comparison between studies.

Nitric Oxide

NO is produced in various tissues in the human body and is an important biological mediator and cell signaling molecule. NO is involved in smooth muscle relaxation, neurotransmission, vasodilatation and host defense reactions [11]. Furthermore, NO can be used to detect inflammation in several hollow organ systems, such as the airways [12] and the intestine [13]. Elevated levels of NO have also been reported in patients with inflammatory disease of the bladder of different etiology such as bacterial cystitis, after Bacillus Calmette Guerain (BCG) treatment for superficial bladder cancer, irradiation and in patients with IC [14].

NO is produced by a family of different nitric oxide synthases (NOS) named after the cells in which they were first found [15]. Endothelial NOS (eNOS) and neuronal NOS (nNOS) are Ca^{2+} dependent and produce small amounts of NO while the inducible NOS (iNOS) is Ca^{2+} independent and can produce large amounts of NO. iNOS was first identified in macrophages and produces high levels of NO as a response to inflammatory signals such as cytokines [16]. NO has a very short half-life, only seconds, in biological fluids but in its gaseous phase it is fairly stable and can easily be measured with chemiluminescence. For measurements of bladder luminal NO a 100 % silicon catheter (Argyle, Sherwood Medical) is introduced into the bladder and 25 mL room air is infused into the catheter balloon. After 5 minutes incubation, the air is aspirated into the syringe and examined in a chemiluminescense NO analyzer. This chemiluminescence assay is highly specific for NO and there is no interference from other nitrogen oxides [17].

NO and Painful Bladder Symptoms/Interstitial Cystitis

In patients with IC the luminal NO levels are significantly increased compared to patients without inflammation of the bladder [14, 18], making it a useful tool in discriminating between patients with painful bladder symptoms of other etiology and those with IC. Furthermore, it is possible to differentiate between classic ulcerous IC and non-ulcerous IC by measuring endogenously formed luminal NO in the urinary bladder [19]. Logadottir et al. showed that patients with non-ulcerous IC did not have elevated levels of NO compared to those with classic IC. This allows classification without performing cystoscopy with hydrodistension and biopsies. Measuring NO in the bladder is a feasible technique and it can also be used in the objective evaluation of different treatments. Hosseini et al. have reported that the NO concentration decreased in patients with IC that had been treated with steroids and that it correlated to a decrease in symptom score in these patients [20].

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It is likely that a major part of the luminal NO measured in the bladder from patients with IC originates from the urothelium. Since NO has a very short half-life in biological tissues it is not likely that NO produced in the deeper parts of the bladder mucosa would contribute to elevated levels of NO measured in the bladder. However, it is possible that inflammatory cells in the bladder wall contribute to the luminal NO measured in patients with IC.

It is still to be elucidated, whether the elevated levels of NO is part of the pathogenesis in IC or simply a part of a secondary inflammatory response. It is also unknown whether the increased NO formation has a damaging or protective role in this disease. The increased NO production may be beneficial in host defence reactions [21], but when produced in excess NO is thought to cause cellular damage [22]. It is possible that a neuroimmune process involving NO may be part of the pathogenesis in IC since evidence has been put forward that nerve fibers and transitional epithelium in the bladder are targets for NO through neurotransmission [23]. Anatomical proximity as well as physiological interactions between mast cells and nerve fibers have been found in bladder tissue of patients with IC [24] and the fact that mast cells harbour many potent inflammatory factors further supports the notion that NO might play an important role in IC pathogenesis.

In conclusion it still remains unknown whether high levels of NO are a part of the pathophysiological mechanisms behind IC and whether high levels of NO have a protective or damaging role in this disease. One can conclude that measuring NO produced in the urinary bladder has provided a new tool for differentiating between IC and painful bladder symptoms of other etiology. Measuring luminal NO is also useful in the differentiation between classic ulcerous IC and non-ulcerous IC and in the objective evaluation of different treatments.

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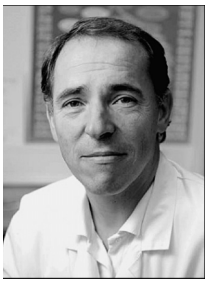

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