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Effects of psychological factors on erectile response to intracavernosal prostaglandin E1.

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Introduction

After the preliminary studies of Virag (1) and Brindley (2), the use of the intra-cavernosal injection of vaso-active drugs (ICI) quickly increased. At present the ICI is widely used both for the diagnosis and for the treatment of male erectile dysfunction (ED)

At least from the clinical point of view, it is often thought that an impaired penile response to ICI suggests a vascular aetiology and that a normal erection in response to ICI suggests a psychogenic or neurogenic cause (3).

However, it has been known for some time that the penile response to this test is variable and somewhat unpredictable; and, in some men with clearly normal sleep-related erections, the occurrence of an impaired response to ICI has been observed, raising the possibility that psychological factors can impair the response to ICI (4, 5, 6).

These data have been obtained mainly from the study of men with psychogenic ED and control subjects.

Meuleman (6) performed a study on 63 men, which involved control subjects and psychogenic, neurogenic and vascular cases. All the subjects underwent ICI on two occasions and with 50 mg. of papaverine both times. Thirty men, i.e. 48%, showed a lower response to the second ICI, which was performed in more stressful conditions.

At present several researchers believe that there is a negative effect of psychogenic factors on the penile response to ICI (5).

There are two main reasons to study the involvement of psychological factors in the response to ICI :

1) first of all, to evaluate the diagnostic limits of the ICI;
2) furthermore, to throw light on the basis of psychogenic ED which might help to improve its pharmacological and psychological treatment.

In '92, two Korean researchers (7) performed a study to evaluate the role of epinephrine (E) and norepinephrine (NE) on the response to ICI. Their protocol involved an ICI of 30 mg. of papaverine in 3 groups of men: 11 control subjects, 60 men with psychogenic ED and 40 with vascular ED; furthermore, the authors split the psychogenic subjects in 2 groups according to their penile response to ICI which was classified as "good" or "poor".

A venous blood collection from the forearm and the penis of the subjects was made 15 minutes after the ICI to assay the systemic and penile plasma levels of E and NE.

The authors observed that the NE plasma level was higher in the penile than systemic blood in all the three groups, but they also found that the penile level of NE was significantly higher in the psychogenic cases than in the normal controls and in the patients with vasculogenic ED. Furthermore, it was significantly higher in the "poor" responders than in the "good" responders within the psychogenic group. No difference was seen for E between the 3 groups.

In conclusion, the authors suggest that the psychological inhibition of the response to ICI is mediated by NE, but the NE would play this role mainly by an increase of its penile tone rather than its systemic tone.

Subjects and methods

We carried out a further study of psychological inhibition of the response to the ICI. Full details of this study are available in the original publication (8). The study involved 59 men (mean age 46.3 years, ±14.48) attending the Sexual Problem Clinic at the Western General Hospital, Edinburgh, and complaining of ED. All the 59 men underwent nocturnal penile tumescence and rigidity (NPT) monitoring for 2 consecutive nights and a morning session after each night which involved ICI only on the second morning (Fig. 1). The ICI was performed with prostaglandin E1 (PGE1), 10 mcg. The night erections and the penile response to the ICI were monitored by RigiScan (9). The state anxiety of the patients immediately before the ICI and their trait anxiety were assessed by self-rating questionnaires. The psychoendocrine indicators of stress before and after the ICI were monitored by the plasma levels of cortisol (C), prolactin (Prl), E and NE (forearm or antecubital vein) and by the urinary excreation of E and NE

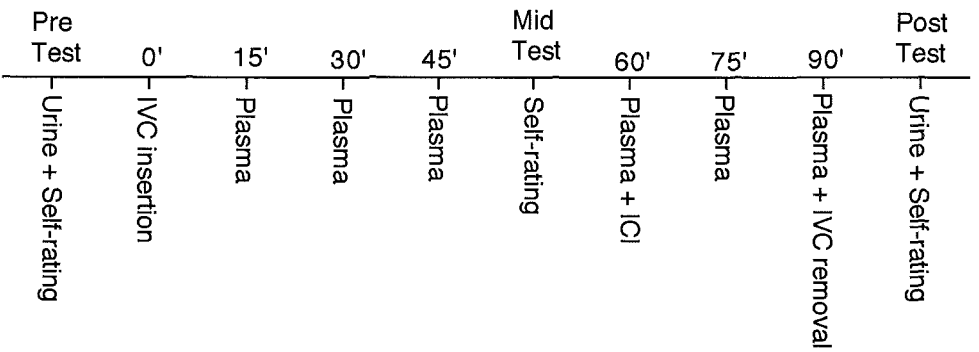

Figure 1. Flow chart of the experimental procedure on each morning. The ICI occurred only on the 2nd and the 3rd mornings. IVC = intra venous cannula.

Before retiring to bed, the patients completed questionnaires concerning trait anxiety, personality and depression (i.e. The Spielberger Trait Anxiety Inventory (10), The Eysenck Personality Inventory (11) and The Beck Depression Inventory (12)).

On each morning immediately after the NPT monitoring, there was a session which lasted 90 minutes. The 2 morning sessions were identical, except that the ICI was given only on the second morning (Fig. 1), so the first morning was used as control. Questionnaires concerning the state anxiety (i.e., The Spielberger State Anxiety Inventory (10), The Stress Arousal Checklist (13) and The Alderley-Parks SAQ (14)) were completed by the patients at pre-test, at mid-test and at post-test. The ICI occurred only on the second morning and immediately after the 60th minute.

In order to quantify the inhibition of the ICI response we took the difference between the maximum increase of penile circumference during the sleep-related erections and the maximum response to the ICI. We called this the "Inhibition Score" (IS). The median of this value has been used to split the subjects in two groups: the High Inhibition group (HI) and the Low Inhibition group (LI).

Twenty one subjects, whose penile response to the first ICI was poor compared to their NPT response, underwent a third morning session identical to the second morning, except that the ICI was performed with a higher dose of PGE1, i.e. 20 mcg. We defined a poor response to ICI as penile rigidity less than 60% and nocturnal penile rigidity more than 25% greater than in response to the ICI.

Hormonal assessment

Urine was assayed for E and NE. Plasma samples were assayed for E, NE, C, Prl (for details of assay methods see (8)).

Results - for whole group

As expected, the HI group has lower mean age (40.7 years $\pm$ 13.9) than the LI group (50.8 years $\pm$ 13.2; p=0.006), consistent with their being more psychogenic cases in this group.

The Spielberger Trait Anxiety Inventory showed higher anxiety in the HI group (p=0.05) (Fig. 2).

No difference was found between the 2 groups with the Eysenck Personality Inventory and the Beck Depression Inventory.

The Spielberger State Anxiety Inventory showed higher anxiety in the HI group during the second morning (p=0.001) (Fig. 2).

The Stress Arousal Checklist showed scores constantly but not significantly higher in the HI group.

The Alderley Parks SAQ did not show different levels of anxiety between the two groups.

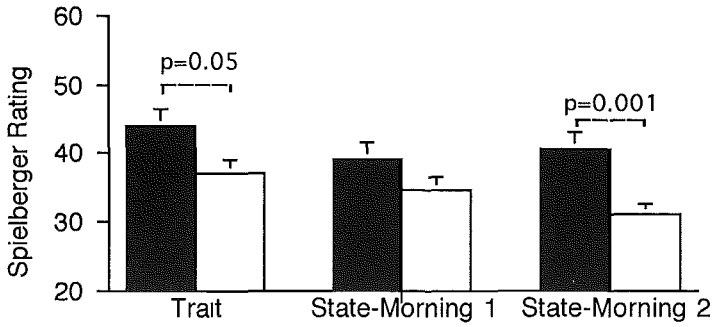

Figure 2. Spielberger Trait and State Anxiety scores for the High ■ (n=28) and Low □ (30) Inhibition Groups.

As far as the neuroendocrine responses were concerned:

For C there was no significant Group effect, but a significant decrease over Time ($p=0.0001$) (Fig. 3). There was also a significant Time x Day interaction ($p=0.029$) and it is noteworthy that, at time 6, C was higher in the HI group on both the mornings, but this was more evident on the second morning. On the second morning, when the ICI was given, both the initial C level (time 1) and the mean C level (mean of 6 samples) correlated with the IS (initial, $r=0.329$, $p=0.017$; mean, $r=0.312$, $p=0.024$). This correlation suggests a link between C and the anticipation of the ICI in the HI group.

Plasma PrI shows a pattern very close to C, with a more evident increase in the last two collections in the HI group during the second morning (Fig. 3). This late increase does not preclude a link with an inhibitory mechanism, but it does not suggest an anticipatory response of PrI.

Both urinary E and NE showed an increase over Time (E, $p<0.0001$; NE, $p<0.0002$), but with no differences between HI and LI groups or between mornings.

For plasma E there was no significant Group effect, but there was a significant Time x Group interaction ($p<0.05$) (Fig. 4). On both days the E levels in the LI group tend to fall, whereas the levels in the HI group tend to rise from time 1 to time 2 and then fall again. The relatively low initial E levels in the HI group might suggest higher distress in this group than in the LI group.

Plama NE levels are constantly lower in the HI group on both the mornings with a significant Group effect ($p<0.05$), however the HI group shows a greater increase on the second morning which is reflected in a significant Day x Group interaction ($p=0.05$) (Fig. 4). It is perhaps possible that in this group there was an increase in NE in the penile blood on the second morning which not only impaired the ICI response but also spilt into the general circulation to cause this rise in systemic NE levels

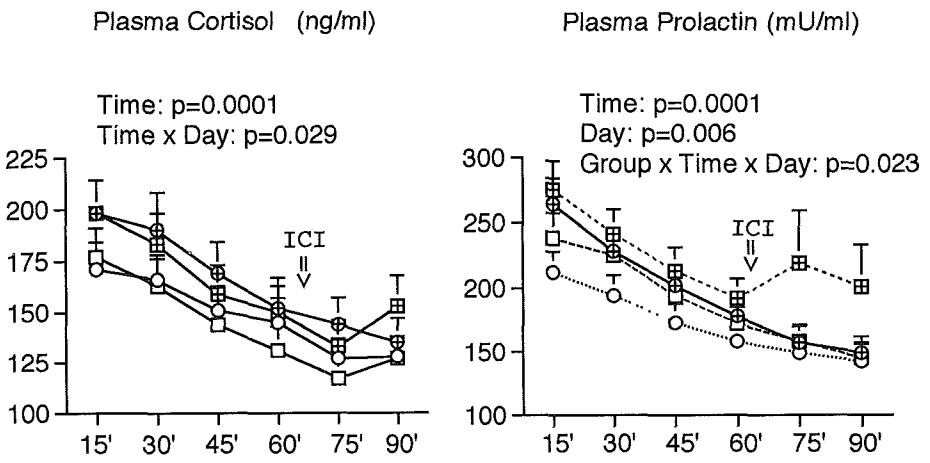

Figure 3. Plasma cortisol and plasma prolactin in High (n=24) and Low (n=28) Inhibition Groups. High Inhibition, Morning 1- —⊕— ; Morning 2- —⊞— . Low Inhibition, Morning 1- —○— ; Morning 2- —□— .

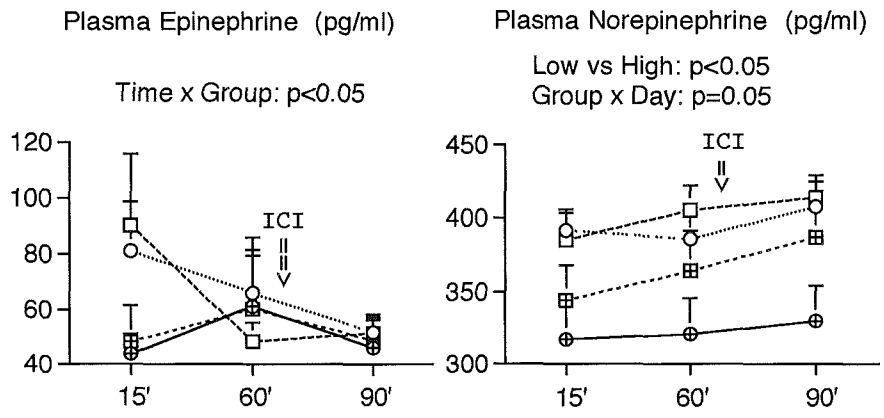

Figure 4. Plasma epinephrine in High (n=21) and Low (n=22) Inhibition Groups. Plasma norepinephrine in High (n=22) and Low (n=25) Inhibition Groups. High Inhibition, Morning 1- —⊕— ; Morning 2- ----⊞---- . Low Inhibition, Morning 1- ·····○····· ; Morning 2- ----□---- .

Sub-group results - the effect of the 2nd ICI

The third test, involving the higher dose ICI, was offered to those subjects who had shown a good NPT response but who had responded badly to the first ICI. Twenty one subjects underwent the third test; 7 were from the original LI and 14 from the original HI groups. The reason for this mixture of subjects from the HI and LI groups on this third morning is that the criteria for offering the second ICI were decided at the start of the study and were based on NPT rigidity scores.The decision to use circumference criteria for the categorisation into HI and LI groups was taken at the end of the study on statistical grounds and methodological grounds; we are now less confident in the validity and reliability of the rigidity measure.

We are therefore presenting analysis of the relationship between change in ICI response with the second injection and change in our various stress measures, taking the 21 subjects as one group. The mean age for this group was 43.0 years $\pm$ 13.0.

There was a significant group improvement in response with the second ICI in both circumference (circumference increase: 1st ICI = 25.8 mm $\pm$ 12.3, 2nd ICI = 35.3 mm $\pm$ 12.7; $p=0.003$) and rigidity ($p=0.001$). However , in 5 subjects the ICI response was worse on the 3rd than the 2nd morning.

State anxiety scores declined from Day 2 to Day 3 ($p<0.05$). For the stress ratings (stress/arousal check list), the only significant change was for the post-test scores, which declined on the third day ($p=0.002$), but as these ratings were made after the response to the ICI was estabilished, this change probably reflected the subjects awareness of their improved response to the 2nd ICI.

Plasma C was significantly lower on Day 3 (Day effect, $p=0.017$; Day 2 v Day 3, $p=0.008$). This partly reflected lower levels throughout the third test, but also the absence of the late increase of C, following ICI, that was seen on the second day.

Plasma Prl was also significantly lower on Day 3 than on either of the other two mornings ($p=0.0001$ in each case).

Urinary catecholamines were markedly higher in the pre-test samples on the third day. This is probably a consequence of the subject having to travel from home to the laboratory for the test, whereas on the first two mornings the tests were carried out in the same building as the sleep monitoring. The mean post-test urinary E levels were identical for the 2nd and the 3rd mornings. The urinary NE however was significantly lower on the third morning than either the 1st or 2nd.

For the plasma catecholamines levels in this subgroup, no significant effects or interactions were found for E. For NE there is a Time x Day interaction ($p=0.035$), reflecting the increase in NE post-test following the ICI on both the 2nd and 3rd morning, although it tends to be lower pre and mid test on the third morning.

Differences between the third morning and the second morning were therefore demonstrated in a number of variables. To examine the relationship with the improvement in ICI response further, the change score from morning 2 to morning 3 for ICI response was correlated with change scores in state anxiety, the increase in stress rating from time 1 to time 2, mean C and Prl levels and post-test urinary NE levels. The only significant correlation was for mean Prl ($r= -0.476$, $p=0.03$).

Conclusion

In conclusion, we have found evidence of stress associated with our testing procedure, in terms of subjective ratings, neuroendocrine measures and urinary catecholamines. However, the ICI added apparently little to the levels of stress, which in several parameters was not significantly higher on the second morning. Furthermore, the improvement in the response to the second ICI could be due to both a reduction in several of our stress measures and the higher dose of PGE1.

We have found no support for the hypothesis that the inhibition of the ICI response is associated with generalised increase in circulating catecholamines. However, we cannot, on the basis of this study, exclude the possibility of an increase in penile NE in our HI group directly accounting for the impaired ICI response.

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Discussion - EFFECTS OF PSYCHOLOGICAL FACTORS ON ERECTILE RESPONSE TO INTRACAVERNOSAL PROSTAGLANDIN E1

K. Demyttenaere

I was very interested about the correlation between anxiety levels and inhibition score. Is there a similar correlation between inhibition scores and levels of cortisol, noradrenaline, etc?

A.R.M. Granata

No, there was not a correlation with the hormonal levels.

G. Wagner

Why did you only test 10 μg of prostaglandin E1? and why did you chose that particular dose?

A.R.M. Granata

We tested also 20 μg. Part of the subjects participated on a second phase of the protocol using a higher dose. These were the subjects who had shown the poorest responses to ICI, after a good NPT. The protocol was the same as that of the first ICI. The Rigiscan values increased during the second ICI, because of the higher dose used. However, the Speilberger anxiety state scores were lower during the second ICI than during the first ICI, so there could be a sum of effects to justify this higher response to the second dose. There were 21 subjects out of 22 that got a better response with the second ICI. When they were asked about this they were pleased with the response they got and in some way they were aroused by the response they got. I think that 10 μg is a low dose, but we tried to be sure in this way that any psychological effect would be apparent instead of being overcome by too a high dose of the drug.

M. Murphy

Did you control for cigarette smoking which can inhibit the erectile response to papaverine?

A.R.M. Granata

Yes we controlled for this. The smokers did not differ from the other subjects in the kind of response, not significantly at least. But anyway they were asked not to smoke during the days of the test. Probably we may derive some data if we compare the results of the third morning, when subjects had not slept at the lab, with those of the first and the second morning when they had.

P. Gutiérrez

Do you think this psychological inhibition is applicable to invasive studies in the diagnosis of erectile dysfunction, such as those involving cavernosography or cavernosometry or even duplex associated with ICI? There is probably a high psychological inhibition in these tests.

A.R.M. Granata

In my experience, if you are just checking vascular problems you can use also a very low dose of PGE1. You just check if there is enlargement of the arteries and improved blood flow to the penis, but you do not need necessarily a good erectile response to say the arteries of your patient are OK.

However, if you focus on the erectile response in a treatment context, I definitely think that psychological factors can have a negative effect on the response. Subjects who routinely resort to self injection report different responses according to the situation, and the response is adversely affected by external stress. Some subjects, who routinely use 10 μg increase occasionally the dose if they feel that they have had an unusually stressing day.

J. Bancroft

The important thing is that these are the very early steps in identifying false negative responses. The diagnostic value of the ICI will be enhanced when we can identify the person who is showing a false negative response. One of the things about Granata's study which interest me is that it fits in with other data that I talked about earlier on psychogenic erectile dysfunction having a sort of subdued catecholamine picture, and rather surprisingly the men with the high inhibition seemed to have lower

catecholamines and certainly low noradrenaline to begin with than the other men. Whether this is part of a pattern of stress response which distinguishes this group of men from others is worth studying.

K.E. Andersson

If this is a reaction to the ICI it would be linked not only to the prostaglandin E1 injections but should also occur, for example, when you inject an alpha blocker. If there is a noradrenergic tone and that tone is being given through alpha adrenoceptors, there should be a better response to a alpha blockers than to prostaglandin E1 in those particular patients, or they should respond to a combination of drugs because prostaglandin E1 inhibits noradrenaline release, particularly in these patients.