Diagnostic Value of Double Injection of Vasoactive Drug in Penile Doppler Ultrasonography

Seung Yon Baek, M.D., Hye Young Choi, M.D., Sun Wha Lee, M.D., Woo Sik Chung, M.D.

Purpose: To evaluate the usefulness of double injection of a vasoactive drug in penile Doppler ultrasonography for the diagnosis of vasculogenic impotence.

Materials and Methods: Eighty-four consecutive cases (bilateral sides) of 42 patients with suspected vasculogenic impotence were included in our study. We used computed sonography (Acuson, USA), with a 7 MHz linear array transducer. After the first intracavernosal injection of the vasoactive drug (10 μg of prostaglandin E1), peak systolic velocity (PSV) and end diastolic velocity (EDV) were measured three times. According to mean PSV and EDV, the patients were classified into four groups: arteriogenic impotence (AI; N = 29), venogenic impotence (VI; N = 28), AI associated with VI (N = 14), and normal (N = 13). After the second injection, PSV and EDV were remeasured, using the same method. Mean velocities of the first injection were compared with those of the second, and the paired t-test was used to analyze the results. The extent to which patients were reclassified after the second injection was noted.

Results: In all four groups, PSV measured after the second injection was significantly different from PSV after the first (P = 0.0001, 0.0001, 0.0010, 0.0072); except in the normal group, EDV measured after the second injection was not different from EDV after the first (P = 0.9815, 0.0654, 0.0950, 0.0057).

After the second injection, the numbers of patients reclassified into other groups were as follows: AI, 11 (38%); VI, 6 (21%); AI associated with VI, 11 (79%); normal, 1 (8%).

Conclusion: Double injection of a vasoactive drug affected PSV, and therefore, appears to be a useful adjunctive procedure for the evaluation of patients in whom classification based on the results of the first injection is difficult.

Index Words: Penis, US
Ultrasound (US), Doppler studies

Penile Doppler ultrasonography after injection of vasoactive pharmacologic agents inducing an erection is important in the diagnosis of vasculogenic erectile dysfunction(1, 2). In 1985, Lue et al. reported duplex ultrasonography as a noninvasive tool in the evaluation of penile circulation(3). The advent of color Doppler imaging allows not only high resolution imaging of vessels and tissue features but also display of flow characteristics and results in rapid and accurate acquisition of Doppler data(4). Increase of arterial inflow and restriction of venous outflow are important to penile erection. Inflow is impaired by atherosclerotic changes in the cavernous inflow tract and veno-occlusive dysfunction occurs when there is anatomical or functional abnormalities of the cavernous body(5). However, sometimes psychic impact may influence to prevent an erection even in the person with normal erectile function. Several pharmacologic agents have been used in
Penile Doppler ultrasonography and these are papaverine hydrochloride, prostaglandin E1, phentolamine mesylate and atropine sulfate (6–9). Many studies included single or combined drugs to evaluate vasculogenic impotence (6–9). But there have been few studies of using double injection of single or combined vasoactive drugs (10, 11). Double injection may relieve or lessen the psychic impact and attain the complete relaxation of penile smooth muscle, therefore it may produce more accurate diagnosis for the vasculogenic impotence.

The objectives of this study are to evaluate whether there are significant differences in the peak systolic and end diastolic velocities between single and double injection of vasoactive drug and whether the method of double injection may influence the diagnosis of vasculogenic impotence.

**Materials and Methods**

Penile Doppler ultrasonography had been performed in 396 cases of 198 patients with suspected vasculogenic impotence during one year and eight months. Out of them, eighty-four consecutive cases (bilateral sides) of forty-two patients with double injection of vasoactive drug were included in our study. The indications of double injection were PSV less than 30 cm/sec and/or EDV more than 5 cm/sec. The patients were 23 to 75 years old (mean, 47 years).

We used an Acuson computed sonography 128 X/P1 0 unit with 7 MHz linear array transducer. Doppler sonography was performed with the patients in supine and penis in the anatomic position. Doppler spectrum was obtained since 3 minutes after first intracavernosal injection of 10 μg of prostaglandin E1 (PGE1) using a 25 gauge needle. Doppler angle was kept less than 60 degrees, sample volume and wall filter were fixed at minimum. The transducer was placed on the ventral side and Doppler spectrum was obtained at the base of the penis where the cavernosal artery angles posteriorly into the crus of the corpus cavernosum. Doppler spectra were obtained three times with 5 minute interval in both sides and peak systolic velocities (PSV) and end diastolic velocities (EDV) were measured and mean velocities were calculated. The patients with less than 30 cm/sec of PSV and/or more than 5 cm/sec of EDV were taken second injection of PGE1 with the same method. PSV and EDV were remeasured with the same method.

According to the results of PSV(normal > 25 cm/sec) and EDV(normal < 5 cm/sec) measured after the first injection of PGE1, the patients were classified into 29 cases of arteriogenic impotence (AI) (PSV < 25 cm/sec), 28 cases of venogenic impotence (VI) (EDV > 5 cm/sec), 14 cases of AI associated with VI (PSV < 25 cm/sec, EDV > 5 cm/sec) and 13 cases of normal. Mean velocities of the first injection (first velocities) were compared with those of second injection (second velocities) and analyzed with paired t-test. We evaluated how many cases of initial groups with the first injection were reclassified into the other groups after the second injection.

**Results**

In all four groups, first PSV after single injection was statistically different from second PSV after double injection (Table 1). In AI group, the first PSV (M = 17.0 cm/sec) measured after single injection was statistically different from the second PSV (M = 25.5 cm/sec) after double injection (P = 0.0001). In VI group, the first PSV (M = 35.3 cm/sec) was different from the second PSV (M = 43.1 cm/sec) (P = 0.0001). In AI associated with VI group, the first PSV (M = 20.7 cm/sec) was different from the second PSV (M = 28.5 cm/sec) (P = 0.0010). In normal group, the first PSV (M = 26.8 cm/sec) was different from the second PSV (M = 33.0 cm/sec) (P = 0.0072). In total 84 cases, the first PSV (M = 25.3 cm/sec) was different from the second PSV (M = 33.1 cm/sec) (P = 0.0001).

The first EDV in each group measured after single injection was not different statistically from the second EDV after double injection except normal group (Table 2). In normal group, the first EDV (M = 2.67 cm/sec) was statistically different from the second EDV (M = 4.62 cm/sec) (P = 0.0101).

### Table 1. Comparison Peak Systolic Velocities after First Injection

<table>
<thead>
<tr>
<th>Group(No)</th>
<th>First PSV</th>
<th>Second PSV</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AI(29)</td>
<td>17.0</td>
<td>25.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>VI(28)</td>
<td>35.3</td>
<td>43.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>AI with VI(14)</td>
<td>20.7</td>
<td>28.5</td>
<td>0.0010</td>
</tr>
<tr>
<td>Normal(13)</td>
<td>26.8</td>
<td>33.0</td>
<td>0.0072</td>
</tr>
<tr>
<td>All(84)</td>
<td>25.3</td>
<td>33.1</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Velocities : cm/second

### Table 2. Comparison End Diastolic Velocities after First Injection with End Diastolic Velocities after Second Injection

<table>
<thead>
<tr>
<th>Group</th>
<th>First EDV</th>
<th>Second EDV</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AI(29)</td>
<td>2.57</td>
<td>2.55</td>
<td>0.9815</td>
</tr>
<tr>
<td>VI(28)</td>
<td>8.02</td>
<td>7.04</td>
<td>0.0654</td>
</tr>
<tr>
<td>AI with VI(14)</td>
<td>6.20</td>
<td>4.93</td>
<td>0.0950</td>
</tr>
<tr>
<td>Normal(13)</td>
<td>2.67</td>
<td>0.87</td>
<td>0.0057</td>
</tr>
<tr>
<td>All(84)</td>
<td>5.42</td>
<td>4.62</td>
<td>0.0101</td>
</tr>
</tbody>
</table>

Velocities : cm/second
different from the second EDV ($M = 0.87 \text{ cm/sec}$) ($P = 0.0057$). In total 84 cases, the first EDV ($M = 5.42 \text{ cm/sec}$) was different from the second EDV ($M = 4.62 \text{ cm/sec}$) ($P = 0.0101$). But in AI group, the first EDV ($M = 2.57 \text{ cm/sec}$) was not different statistically from the second EDV ($M = 2.55 \text{ cm/sec}$) ($P = 0.9815$). In VI group, the first EDV ($M = 8.02 \text{ cm/sec}$) was not different from the second EDV ($M = 4.93 \text{ cm/sec}$) ($P = 0.0950$).

After double injection of vasoactive drug, out of 29 AI patients, five patients (17%) were reclassified into normal (Fig. 1) and six (21%) into VI, therefore total 11 patients (38%) of AI were reclassified. Out of 28 VI patients, five patients (18%) were reclassified into normal (Fig. 2) and one (4%) into AI and total six (21%) were reclassified. Among 14 patients with AI associated with VI, four (29%) were reclassified into normal and four (29%) into AI and three (21%) into VI, therefore 11 patients (79%) were reclassified. Among 13 normal persons, one person (8%) was reclassified into AI. Therefore, 29 of 84 cases (35%) in all four groups were reclassified into other groups (Table 3).

### Discussion

Erectile dysfunction defined as an inability to generate or maintain an erection adequate for sexual activity results from organic disease in 50—90% of cases (12, 13). Most cases are a result of hemodynamic dysfunction with arterial and/or venous incompetence. The parameters to indicate arterial disease are subnormal clinical response to vasoactive drug, little or no arterial dilatation and a peak systolic velocity less than 25 cm/sec (3, 14). Mean end-diastolic velocity greater than or equal to 5 cm/sec should be considered as venogenic impotence (4, 15).

Hemodynamic changes in the erectile response reveal relaxation of the smooth muscle of the cavernosal arterioles and sinusoids, resulting in their dilatation and an increase in blood flow. The filling and distension of the sinusoids against the indistensible tunica albuginea results in the mechanical compression of the draining venules between the sinusoidal walls and the tunica, effectively restricting venous outflow (12).

### Table 3. Reclassification of Groups after Double Injection

<table>
<thead>
<tr>
<th>Initial Group</th>
<th>AI</th>
<th>VI</th>
<th>AI with VI</th>
<th>Normal</th>
<th>Reclassified</th>
</tr>
</thead>
<tbody>
<tr>
<td>AI (29)</td>
<td>18 (62%)</td>
<td>6 (21%)</td>
<td>0 (0%)</td>
<td>5 (17%)</td>
<td>11 (38%)</td>
</tr>
<tr>
<td>VI (28)</td>
<td>1 (4%)</td>
<td>22 (78%)</td>
<td>0 (0%)</td>
<td>5 (18%)</td>
<td>6 (21%)</td>
</tr>
<tr>
<td>AI with VI (14)</td>
<td>4 (29%)</td>
<td>3 (21%)</td>
<td>3 (21%)</td>
<td>4 (29%)</td>
<td>11 (79%)</td>
</tr>
<tr>
<td>Normal (13)</td>
<td>1 (8%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>10 (92%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>All (84)</td>
<td>24 (29%)</td>
<td>31 (38%)</td>
<td>3 (4%)</td>
<td>24 (29%)</td>
<td>29 (35%)</td>
</tr>
</tbody>
</table>

Fig. 1. 40 year old male with suspected vasculogenic impotence.

**A.** The peak systolic velocity (PSV) and end diastolic velocity (EDV) of first injection of vasoactive drug revealed 20 cm/sec and 2 cm/sec respectively, suggesting arteriogenic impotence.

**B.** PSV and EDV after second injection revealed 28 cm/sec and 0 cm/sec respectively, suggesting normal range. Therefore arteriogenic impotence after first injection was reclassified into normal after second injection.
Normal erectile function requires normal vasculogenic, neurogenic and psychogenic factors. For the patient suggestive of erectile dysfunction, neurogenic and endocrine abnormalities can be evaluated through clinical history, endocrine assays and physical examination(16). The evaluation of hemodynamic factors requires a more invasive analysis of arterial flow and venous competence by means of internal pudendal arteriography and dynamic infusion cavernosometry. The arteriography with vasoactive drug injection is considered as gold standard for the evaluation of penile inflow and provides accurate anatomical information, but this study is invasive, expensive, time-consuming, and painful(16). There are a variety of ways to analyze arterial inflow indirectly, including Doppler sonography, plethysmography and penile blood pressure measurement(17).

Duplex Doppler ultrasonographic assessment of penile blood flow is one of the best screening tools currently available(1, 2) and replaces the selective arteriography progressively. Several studies have revealed that penile Doppler ultrasonography correlates with selective arteriography with 90—95% of the cases(18, 19). In addition, the advent of color flow has been useful in detection and visualization of some smaller cavernosal arteries(6).

Many investigators proposed various cutoff values for differentiating normal from vasculogenic impotence. The proposed value of peak systolic velocity include 25 — 40 cm/sec(1, 2, 4, 12, 20, 21) and the upper normal limit of end diastolic velocity is 5 cm/sec(4, 15). The broad range of cutoff values may be explained by variety of standards for arterial function, differences in the study population, intrinsic differences among types of equipment, inappropriate angle of insonation, inherent diffraction and side-lobe artifact(1, 15). We have used 25 cm/sec as the lower normal range of PSV and 5 cm/sec as the upper normal range of EDV. There is no reports about diagnostic cutoff values of the peak systolic velocity and the end diastolic velocity for double injected cases. Therefore, we used same cutoff value of normal velocity in single injection as well as in double injection.

Various technical modifications for Doppler ultrasonography have been introduced, such as the type and dose of vasoactive drugs, the time interval between intracavernosal injection of vasoactive drug and Doppler examination, the indices and the sampling location measured on Doppler spectral analysis(13, 22, 23).

Psychological factors influence peak velocity measurement and waveform progression(1, 15). In very anxious patients, sympathetic discharge prevent dilatation of the cavernosal arteries in response to vasoactive drug and cavernosal arterial value may suggest arterial insufficiency erroneously. To overcome the vasoconstriction in anxious patient, adequate dosing such as multidosing of single or combined drugs was injected intracavernosally to decrease sympathetic outflow and then the evaluation of erectile dysfunction could be enhanced(10, 11). Katlowitz et al(10) reported that overall response to multidosing was 51.5%(17/33) of their cases. In our study, by means of double injection of vasoactive drug, patient’s anxiety
and vasoconstriction might be overcome. Therefore the first PSV after single injection was statistically differ-ent from the second PSV after double injection and 29 of 84 arteries(35%) were reclassified into the other groups. But EDV after first injection was not different statistically from EDV after second injection except normal person. Although there was no statistical signif-icance between the first and the second EDV of VI group, five of 28 patients(18%) were reclassified into normal group.

Most reports using vasoactive drug in the diagnosis of vasculogenic impotence was used either a single drug or combination of several drugs(6). Several studies reported that multiple vasoactive drugs which exerted their effects through different mechanisms of action produced a pharmacologic synergism(7—9). Some studies indicated that prostaglandin E1 might be better than papaverine or papaverine/phentolamine (24,25). Pharmacologic effect of prostaglandin E1 has alpha blocking properties mediated through a mem-brane receptor and relaxes the cavernous and arteriolar smooth muscle through c-AMP pathway while causing a restriction of venous outflow(14,26). In our study, prostaglandin E1 was used and some patients felt discomfort after intracavernosal injection but complications were not found.

The first limitation of our study is that only velocity of cavernosal artery according to spectral wave analy-sis on the Doppler ultrasonography was used as the di-agnostic criteria for the vasculogenic impotence. We did not perform internal pudendal arteriography and cavernosography as the gold standards for diagnosis of vasculogenic impotence, because these were invasive, painful and time consuming methods. Several studies revealed that Doppler ultrasonography was a best screening tools and well correlated with the findings of the selective arteriography, therefore, the other imaging or functional studies were not combined in our study. The second limitation is that diagnostic cut-off value of velocity in the double injection have not been established yet. Although we could conclude that peak systolic velocity after first injection was signifi-cantly different from those after second injection, we could not conclude that the results of double injection might be more accurate than those of single injection. Therefore, further study for normal range of velocity should be done in the patients with double injection. The third limitation is small numbers of the materials. Total number of our study is 84 cases of 42 patients, so further study must be needed.

In conclusion, double injection of vasoactive drug was effective to PSV and therefore, it seems to be ad-junctive method for the evaluation of the patients who are considered equivocally as AI or AI combined with VI after first injection.

References

외래부위의 진단적 가치

목적: 발기유발약제를 이중주사한 후에 실시한 음경도플러초음파검사가 혈관성발기부전을 진단하는데 유용한지 알아보기로 하였다.

대상 및 방법: 혈관성발기부전이 의심되어 음경도플러초음파검사를 실시하였던 연속적인 환자 42명의 양측 음경해면체동맥 84예를 대상으로 하였다. 사용한 초음파 기기는 Computed sonography(Acuson, USA)이며 7 MHz의 선형탐촉자를 사용하였다. 발기유발약제로 prostaglandin E1(PGE1) 10μg를 음경해면체내에 첫번째 주사한 후에 양측 음경해면체 동맥에서 최고수축기유속(PSV)과 확장말기유속(EDV)을 각각 세번 측정하였다. 평균유속에 따라 대상을 동맥부전군(N=29), 정맥부전군(N=28), 혼합군(N=14)과 정상군(N=13)으로 나누었다. 동량의 PGE1을 두번째 주사한 후에 PSV와 EDV를 같은 방법으로 측정하였다. 첫번째 주사주의 평균 PSV, EDV와 두번째 주사주의 평균PSV와 EDV가 차이가 있는지 t 검정을 이용하여 분석하였다.

또한 첫번째 주사후에 측정된 유속에 따라 분류된 네군 각각에서 두번째 주사후의 변화된 평균유속에 따라 다른군으로 얼마나 재분류되었는지를 알아보았다.

결과: 네군 각각에서 두번째 PSV는 첫번째 PSV와 동계학적으로 의미있게 차이가 있었다(P=0.0001, 0.001, 0.0010, 0.0072). 그러나 EDV는 정상군을 제외하고는 두번째 EDV와 첫번째 EDV간에 동계학적으로 차이가 없었다(P=0.9815, 0.0654, 0.0950, 0.0057).

두번째 주사주의 평균 PSV와 EDV의 수치에 따라 동맥부전군의 11예(38%), 정맥부전군의 6예(21%), 혼합군의 11예(79%)와 정상군의 1예(8%)가 다른 군으로 재분류되었다.

결론: 발기유발약제의 이중주사법은 PSV에 영향을 미치므로 첫번째 주사후 동맥부전군과 혼합군으로 평가된 환자에서 최종 진단이 애매한 경우에 부가적인 검사로 사용될 수 있으리라고 생각된다.