Original Article

Effects of Transdermal Therapeutic System-Nitroglycerin in Patients with Heart Failure. Influence on Hemodynamic Changes

Eiji INO-OKA, Tamotsu TAKISHIMA*, Kogo ONODERA**, Masataka KATO***, Masato HAYASHI**** and Shouji YASUI+

Fourteen patients suffering from severe heart failure with 18 mmHg or higher diastolic pulmonary arterial pressure were given a transdermal therapeutic system of nitroglycerin (TTS-NTG). They were evaluated for changes in the hemodynamic responses over 24 hours. Diastolic pulmonary arterial pressure decreased from 27.1± 2.3 mmHg (mean± SE) to 22.4± 1.7 mmHg after 1 hour (p <0.01), which was maintained throughout the trial. Cardiac index increased from 2.42 ± 0.13 1/min/m² to 2.64 ± 0.16 1/min/m² after 1 hour (p <0.01). The analysis of cardiac and vascular function curves in individual patients suggested that the improvement of hemodynamics was induced mainly in six patients with an increase of contractility and in four patients with a reduction of afterload. No changes were observed in three patients in either contractility or afterload, and a decrease in contractility was seen in one patient. These results suggest that TTS-NTG can be transcutaneously absorbed well enough to produce improved hemodynamic responses in patients with severe heart failure by several mechanisms and maintain these effects over 24 hours.

Key words: Heart failure, Hemodynamic changes, Nitroglycerin, Transdermal therapeutic system

Nitroglycerin (NTG), as a vasodilator therapy, has been used in the treatment of angina pectoris as well as of heart failure (1-6). It dilates not only coronary vessels, which may result in enhanced contractility by increasing coronary blood flow (CBF), but also capacitance vessels, which cause a pooling of blood in the peripheral venous system resulting in a relief of pulmonary congestion, and again resistive vessels, which may result in an increase in cardiac output by reducing afterload with an ultimate alleviation of the cardiac failure state.

Our experimental studies suggested, however, that inadequate use of a vasodilator may induce further worsening hemodynamics by decreasing contractility due to reduced coronary perfusion, and by shifting the cardiac function curve leftward due to lowering of circulatory blood volume (2, 7-10).

In fact, several studies suggested that there were some patients who failed to induce beneficial effects, induced rather an adverse hemodynamic condition by vasodilator therapy (11-18), or developed an early disappearance of beneficial hemodynamic effects (14-16, 19, 20).

For the explanation to these controversial responses, early development of tolerance (14-16, 19, 20), inadequate absorption to the target organ and failure of vasodilation due to pronounced edema or due to mild vessel disease (13-14) have been...
reported.

On the other hand, theoretical and experimental studies have shown that different results are induced depending on the conditions of preload, afterload, cardiac contractility, circulating blood volume, vascular tone of peripheral and central venous pooling system (2, 7–10), and suggested that to analyze the effect of nitroglycerin on those factors is useful not only for evaluating the clinical effects but also for clarifying the mechanism of different responses to patients with heart failure.

In general, however, the Forrester’s subset is used for evaluation and detailed analyses of those factors have not been reported due to difficulty of estimation. We assumed that the relative change in cardiac and vascular function curves (C, V) can be estimated from the data measured by Swan-Ganz catheter technique qualitatively with some limitations.

We have thus studied the effects of NTG on hemodynamics in patients with severe heart failure and attempted to analyze the relative change in C and V. For this purpose, we have used TTS-NTG (CIBA-GEIGY Limited), with which high and stable serum concentration level of NTG can be obtained over 24 hours (19, 21).

**METHODS**

Patients selection: Fourteen patients with diastolic pulmonary arterial pressure (dPA) over 18 mmHg who had clinical manifestations of congestive heart failure were treated with TTS-NTG. The clinical characteristics of the patients and their baseline hemodynamics are shown in Table 1. Eleven men and three women aged 17 to 82 years (average 57.9 ± 5.1 years) were studied. The underlying diseases were ischemic heart disease in seven patients (acute myocardial infarction in three, old myocardial infarction in four), valvular disease in three, con-

<table>
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<th>Patient</th>
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<th>Age (yr)</th>
<th>Cause of HF</th>
<th>NYHA classification</th>
<th>Dose of TTS-NTG</th>
<th>Concomitant drugs</th>
<th>dPA (mmHg)</th>
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| Mean    | —    | 57.9    | —            | —                   | —               | 27.1              | 22.4 | 21.9 | 21.2 | 21.2 |
| S E     | —    | 5.1     | —            | —                   | —               | 2.3               | 1.7  | 2.1  | 2.4  | 2.0  |

gestive cardiomyopathy in three, and hypertensive heart disease in one. The mean baseline dPA was 27.1 ± 2.3 mmHg and the mean baseline cardiac index (CI) was 2.42 ± 0.13 l/min/m².

Most of the patients had been treated with diuretics and/or digitalis before starting the trial. The degree of heart failure based on NYHA was class 4 in nine patients, 3 in three patients and 2 in two patients. Nine patients were treated with diuretics and digitalis before and during the trial in the same dose, and five patients with only TTS-NTG. Informed consent was obtained from each patient or family.

Administration: Patients were treated by only single application of TTS-NTG (supplied by CIBA-GEIGY Limited). The site of application was on the chest. The drug for use was TTS-NTG 25 mg/10cm² containing 25 mg of NTG, and TTS-NTG 50 mg/20cm² containing 50 mg of NTG was used only in one patient. The NTG-release areas of these patches are 10 cm² and 20 cm², respectively. NTG is absorbed transcutaneously, releasing approximately 20% of NTG over a 24-hour period. According to Nakashima’s study (22) on application of TTS-NTG in healthy Japanese volunteers, it was shown that the mean serum concentration of NTG was 0.13 ± 0.02 ng/ml for 25 mg/10cm², and 0.26 ± 0.04 ng/ml for 50 mg/20cm², respectively, plasma concentration rose clearly at 1–2 hours after application of the patches while the concentration was maintained at a steady level all throughout the application and that when the patch was removed, NTG in plasma disappeared within an hour.

### PROCEDURES AND PROTOCOL

Hemodynamic measurement: Right heart catheterization was performed percutaneously with a Swan-Ganz thermodilution catheter, and

<table>
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<th>mBP (mmHg)</th>
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<th>Side effects</th>
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<td>C 1 2 4 24(hr)</td>
<td>C 1 2 4 24(hr)</td>
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<td>105</td>
<td>91 101 103 95 2.85 3.60 3.82 2.67 2.70 redness, itching</td>
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<td>91</td>
<td>90 86 98 — 2.22 2.28 2.03 1.92 — redness, itching</td>
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<td>80</td>
<td>82 80 79 80 1.65 2.09 2.05 2.01 2.00 —</td>
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<td>81 85 91 88 2.33 2.38 2.88 2.51 2.11 —</td>
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pulmonary arterial pressure (PA) and cardiac output (CO) were determined. Heart rate (HR) was obtained from ECG and systemic blood pressure (BP) was measured by sphygmomanometer.

Pressures and CO were measured twice before the treatment at 30 minutes' intervals to confirm a steady state. The following hemodynamic parameters were determined and analyzed statistically: dPA (mmHg), CI (CO divided by body surface area, ml/min/m²), mean blood pressure (mBP: diastolic blood pressure plus one-third of the pulse pressure, mmHg), stroke index (SI: CI divided by HR, ml/beat/m²), stroke work index (SWI: SI multiplied by subtracting dPA from mBP, g-M/beat/m²), systemic vascular resistance (SVR: mBP divided by CO, dyne · sec/cm²), pulmonary vascular resistance (PVR: mPA minus dPA over CO, dyne · sec/cm²). Each parameter was monitored 0, 1, 2, 4 and 24 hours after application.

Assessment of C and V: The change in CI and dPA was plotted on x-y coordinates from control (0), one (1), two (2), four (4) and 24 hours (24) after treatment.

Considering the relationship of cardiac output and venous pressure shown in the report of Berne and Levy (23), we draw C and V as follows: 1) dPA and mBP can be regarded as an index of preload and afterload, respectively. 2) Heart is working at the equivalent point (crosspoint) of C and V. 3) V moves parallel to the horizontal axis when blood volume or venous vascular bed is changed. 4) C moves parallel to the vertical axis when afterload is changed. 5) C also moves upward or downward associated with change in slope when contractility is changed. For example, in patient No. 3 shown in Fig. 2, the relationship between CI and dPA changed from 0, 1, 2, 4 and 24 at each period. At first, Vo and Co were drawn arbitrarily by referring to the data in the case of severe heart failure (Fig. 1) (23). The mBP is also represented at the upper right of C. Then V₁, V₂, V₄ and V₂₄ were drawn parallel to V₀ on each point. At one hour after treatment, a marked reduction of dPA was induced by dilatation of venous vascular bed and a slight increase in CI, might be induced by reduction of afterload (from

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**Fig. 1.** Cardiac and vascular function curve in heart failure. With moderate or severe heart failure, the cardiac function curves are shifted to the right. With no change in blood volume, cardiac output decreases and venous pressure rises (from control equilibrium point A to point B or point C). With the increase in blood volume that usually occurs in heart failure, the vascular function curve is shifted to the right. Hence venous pressure may be elevated with no reduction in cardiac output (point D) or (in severe heart failure) with some diminution in cardiac output (point E) (23).

**Fig. 2.** Relationship between CI and dPA in patient No. 3.

**Fig. 3.** Effects of TTS-NTG on hemodynamic parameters. dPA decreased significantly one hour after application and persisted for 24 hours. CO, CI and SI increased significantly one or two hours after application, then returned gradually to the baseline levels. Other parameters did not show significant changes. Comparisons of the data at each time with control were analyzed by paired t-test. +: p<0.1, *: p<0.05, **: p<0.01

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77 to 71) with a slight increase in contractility. Thus $C_1^{71}$ was drawn with a slightly increased slope than $C_0$. If not, this point should be at $C'0$. At two hours after application, a further increase in CI resulted in a slight decrease in vascular bed ($V_2$) and a slight increase in afterload (79), which were similar to the levels in the control. So, if contractility is at the same level as in the control, the equivalent point should be at the level lower than $C''0$. Thus we expect that if the increase in contractility is induced, $C_2^{79}$ will be drawn with a much higher slope than $C_1^{71}$. At 24 hours after application, CI increased further with a decrease in afterload. Thus we drew $C_2^{70}$ with parallel to $C_2^{79}$.

In summary, in this case, contractility increased markedly with an increased in venous vascular bed and a slight decrease in afterload. All fourteen patients were analyzed by this method.

Data were analyzed by paired t-test, analysis of variance (ANOVA) and Scheffe type multiple comparison. Each value was represented as the mean ± standard error. The level of significance was set at $p < 0.05$.

RESULTS

Hemodynamic effects: The changes of hemodynamic parameters in all patients given as mean ± standard error at the prescribed intervals of time are shown in Fig. 3. dPA decreased from 27.1 ± 2.3 mmHg to 22.4 ± 1.7 mmHg during the first hour and this reduction persisted over 24 hours. CO, CI and SI showed a significant increase from 3.79 ± 0.25 to 4.13 ± 0.29 l/min, from 2.42 ± 0.13 to 2.64 ± 0.16 l/min/m² and from 27.5 ± 1.7 to 31.1 ± 2.5 ml/beats/m² at maximum levels, respectively. These occurred transiently between 1 and 2 hours after application, thereafter reducing gradually to the baseline levels.

SVR also transiently decreased from 2071 ± 156 to 1866 ± 177 dyne-sec/cm² at maximum levels 1 hour after application, thereafter returning gradually to the baseline. BP, HR, SWI and PVR did not change significantly throughout the trial. The relationship between the mean values of dPA and CI is illustrated in Fig. 4. The values remained in Class III of Forrester’s subset throughout the trial. However, CI increased during the first hour after application, thereafter reducing to the baseline level, while dPA showed a further reduction 24 hours after application than the levels 1 and 2 hours after application. In Figs. 5-a, b, c, the relative changes in C and V which were seen. In six of the fourteen patients, shown in Fig. 5-a (group C), we assumed that the main effect of NTG was induced by enhanced contractility with increased vascular bed. In four patients shown in Fig. 5-b (group A), afterload reducing with increased vascular bed but without changing contractility is the main effect of NTG. In three patients (Nos. 2, 6 and 9) in Fig. 5-c (group N), NTG increased venous vascular bed (in patient No. 9, the effect was only transient). In patient No. 14, venous vascular bed was decreased or increased depending on the circulating blood volume, and contractility was increased 2 hours after application but decreased 24 hours after application.

In Fig. 6, the mean values of dPA, mBP and CI in the controls and those after treatment in each group are presented. In the controls, no significant differences were seen in all three parameters of each group. In the groups C and A, dPA decreased significantly but in the group N, no change was seen after treatment. mBP also decreased more significantly in the group A than in the other two groups. CI increased only in the group C significantly and decreased significantly in the group N (Fig. 5), where as no significant change was induced in the group A.

As for side effects, both topical redness and itching appeared in two out of the 14 patients.
Fig. 5-a. Relative change in C and V in group C.
(14.3%); these side effects were slight. There were no patients withdrawn from the trial because of side effects or aggravated symptoms.

**DISCUSSION**

The beneficial effects of nitrate therapy in patients with congestive heart failure are widely recognized (1-6, 17, 18). However, the hemodynamic responses with the pharmacological properties of the drug administered and the hemodynamic subsets of the patients being treated are controversial (11-18).

A significant decrease in pulmonary capillary wedge pressure, concomitant with a reduction in arterial pressure has been reported with intravenous (3, 24, 25) and sublingual nitrates (11, 17, 24-26). A relatively small decrease or increase in CI has also been reported (16, 26, 27). Our study also showed that NTG reduced dPA significantly over 24 hours while it increased CI transiently, which returned to the baseline at the end of study. Some studies suggest that the stroke volume after nitrate increases in the patients with dPA over 15 mmHg and decreases in the patients with a lower dPA (18). Our results are partially consistent with the results mentioned above. That is, NTG appeared to be more effective in the patients with dPA over 25 mmHg: CI was increased and dPA was decreased, both to significant levels in our study.

**Different response to NTG in dPA and CI**

The reason why NTG is effective in decreasing
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Fig. 5-c. Relative change in C and V in group N.

dPA but not effective enough in increasing CI over 24 hours is unclear. Jordan et al (27) reported that extremely high doses of NTG are required to produce an increased CI as well as a consistently lower PCWP. They suggested that an adequate transdermal absorption of NTG may not be feasible in some patients at low doses because of great individual variances in response and we also suggested that high doses of NTG are required to reduce PCWP by 30% to increase CI.

In fact, some patients, though only a few, failed to respond to TTS-NTG, suggesting that the dose of TTS-NTG was too low, due to a failure of drug absorption in heart failure or to a poor response of the patients in our series. And also patients who showed dPA over 25 mmHg at the baseline induced a reduction of dPA by 30% with an increase in CI. However, many patients who did not show dPA over 25 mmHg revealed a transient increase in CI during the trial with a small reduction in dPA. There also were some patients who showed a reduction in CI with a 30% lowering of dPA. Thus the need for a 30% PCWP reduction is questionable.

As another possible reason, Olivari (19), Rajfer (20) reported that the hemodynamic changes returned to the baseline levels 24 hours after application, suggesting the rapid development of tolerance to NTG. This can be explained partly because the dPA lowering effect persisted for 24 hours in our trial while the maximum effect was seen 1 and 2 hours after application. However, this does not clarify the different response to dPA and CI. Our
Fig. 6. Mean values of hemodynamic parameters in each group. Each hemodynamic parameter at control and treatment-period was shown in the upper figure. Comparisons within groups were analyzed by paired t-test. +: p<0.1, *: p<0.05, **: p<0.01.

Results of comparisons of each hemodynamic parameter at control and treatment-period between groups were shown in the lower figure. Data were analyzed by ANOVA and comparisons between each group were analyzed by Scheffe type multiple comparison.

study and Sharpe's (28) suggest that the effects of TTS-NTG may persist over 24 hours.

We assumed that the different response to dPA and CI may come from the different response to contractility, afterload and preload in each patient as seen later.

Analysis of relative change in C and V

Although the beneficial effects of NTG on heart failure have been reported, the reason not only for the different response to dPA and CI but also for the main mechanisms inducing such effects remains unclear.

We thus studied a relative change in C and V to estimate a change in relationship between the afterload, preload, contractility and CI. With many assumptions, only the qualitative estimation was made; so the analysis had some limitations. In this study at 24 hours after application, 12 of the 14 patients showed that NTG dilated a venous vascular bed shifting a V leftward, where as the remaining two (Nos. 9 and 14) did not.

The main effects of NTG were observed in six patients showing the increased contractility and in four patients showing the reduced afterload. The former six patients developed the beneficial effects both on dPA and CI. On the other hand, the remaining eight patients showed random responses, that is, CI was increased transiently and then returned to the baseline level in six patients, and CI was increased in one patient (No. 5) and decreased in one patient (No. 9). As expected from the Frank-Starling mechanism, when contractility remains unchanged, CI was decreased with a decrease in preload. We should therefore take care to keep the most adequate hemodynamics, especially to get adequate blood volume in a patient who showed such behavior. Only one patient (No. 14) showed that NTG induced the decreased contractility at the end of the trial. V of this patient shifted
rightward unexpectedly. We assumed that increased blood volume or unexpected venoconstriction was the reason. Such phenomenon was seen transiently in patient Nos. 2 (2) and 10 (4), and at the end of trial in patient No. 12 probably due to over transfusion. In all those patients, as contractility remained unchanged or enhanced, elevated preload resulted in increased CI.

We analyzed the hemodynamics at the control condition of each group which was classified by its response to NTG. Although we could not predict the effects of NTG from the controlled hemodynamics, however, those analyzed data suggested that whether or not NTG increases CI mainly depends on whether or not NTG can increase the coronary blood flow, reduce the myocardial oxygen consumption with improved intramyocardial blood flow distribution by preload reduction and enhance the contractility as shown by experimental studies (2, 7, 9).

Limitations of this analysis

As mentioned above, this analysis contained some assumptions and limitations. Without measuring the blood volume directly, we drew Vo and Co arbitrarily by following others' reports. V shifted leftward parallel to the horizontal axis when the absolute value of blood volume decreased (due to hemorrhage, dehydration) or the relative value of blood volume to vascular bed decreased with the increase in venodilatation. The slope of V changed with the alteration of peripheral resistance, but this effect was ignored to avoid the complexity of analysis. Further, the degree of parallel shifts of C due to change in afterload and the degree of slopes of C due to change in contractility were taken arbitrarily. Consequently, our data can be used only qualitatively.

This limitation is crucial for understanding the cardiac and vascular functions of each patient and requires to measure the cardiac and vascular function curves at every point of time. However, our primary purpose of this study is to clarify the mechanism of NTG as a vasodilating agent for treatment of cardiac failure and also to clarify the reason why NTG produced a discrepancy in effect between CI and dPA. This quantitative technique seems to show us enough results to answer our purpose.

The concepts mentioned above have been proposed from theoretical and experimental view points. However, clinical application of those concepts has not been reported.

Although some limitations exist in this analysis, we expect that the results may contribute to clarify a possible mechanism of vasodilator therapy and may also be useful to treat patients with heart failure most effectively and safely on vasodilator therapy.

In conclusion, our trial has revealed that TTS-NTG can produce beneficial hemodynamic effects in patients with relatively higher dPA by increasing contractility and vascular bed, and that the duration of action is relatively long to allow the once-daily application.

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