Preliminary Report

Effects of Combined Sildenafil-Nitric Oxide Donor On Defibrillation Efficacy

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Background: *A previous study demonstrated that supra-therapeutic concentration of sildenafil citrate attenuates defibrillation efficacy. However, the effect of combined sildenafil and NTG administration on defibrillation efficacy is not known.*
Objective: *The present study investigated whether sildenafil administration at the therapeutic level increases the defibrillation threshold (DFT) when combined with NTG.*
Material and Method: *Twenty-four pigs (20-25 kg) were randomized into four groups. After the control DFT was obtained, a stock solution of 50-mg (group 1, therapeutic concentration) and 100-mg (group 2, supra-therapeutic concentration) of sildenafil, and 100-mL of saline (groups 3 and 4) were infused at 2 mL/min. Then, NTG was administered in groups 1-3 at 5 □g/min, with an increment of 5 □g/min every 5 min. The DFT was determined again after NTG was infused for 20 minutes.*
Results: *In group 1, the DFT (402 ± 33V, 11 ± 2J) was not different from the control (404 ± 28V, 11 ± 2J). In group 2, the DFT (521 ± 18V, 19 ± 1J) was higher ($p < 0.004$) than that in the control group (444 ± 31V, 14 ± 2J). Saline did not alter the DFT, either individually or in combination with NTG.*
Conclusion: *Supratherapeutic dose of sildenafil-NTG combination significantly increased the DFT (17% of peak voltage, 37% of total energy). This effect on DFT appears to be driven by sildenafil and not NTG.*

Keywords: *Sildenafil citrate, Nitroglycerin, Fibrillation, Defibrillation*

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Sildenafil is a highly selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE-5), which is used for the treatment of Erectile Dysfunction (ED)[1-5]. Growing evidence has also demonstrated that sildenafil is an effective agent for treating pulmonary arterial hypertension, leading to an increased use of this drug[6-9]. PDE-5 is found not only in the vasculature of the corpus cavernosum, but also in the systemic arteries and veins throughout the body[10]. Accordingly, PDE-5 inhibitors are effective as mild vasodilators by increasing intracellular cGMP levels in vascular smooth muscle[11].

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Although sildenafil has been used clinically for many years, its cardiac effects are still unclear and need to be investigated further[12-14]. In clinical use since 1998, PDE-5 inhibitors have an excellent safety profile, and it is now clear that sildenafil is not arrhythmogenic at the therapeutic level[15-17]. However, it has been reported that some of the patients who died suddenly, presumably by fatal ventricular arrhythmia, were on sildenafil in combination with nitrate therapy[18]. Furthermore, administration of sildenafil together with nitric oxide donor at the supra-therapeutic level has demonstrated the promotion of fatal arrhythmias, whereas sildenafil alone at the therapeutic level is not arrhythmogenic[19]. Recently, we demonstrated that defibrillation efficacy was significantly attenuated when sildenafil was administered intravenously at the supra-therapeutic level, but not at a therapeutic dose[20]. Since nitroglycerine (NTG) is known to have a synergistic

effect on blood pressure when given with sildenafil[21], and sildenafil administered in combination with nitric oxide donor promotes fatal arrhythmias[19], the authors sought to determine whether combined sildenafil-NTG administration significantly affected the defibrillation threshold (DFT) when sildenafil is administered at the therapeutic level. In the present study, the authors tested the hypothesis that intravenous administration of sildenafil at a therapeutic dose, together with NTG, attenuates defibrillation efficacy.

Material and Method

Animal preparation and electrode placement

Experiments were performed on the swine model; twenty-four healthy pigs (20-30 kg) of either sex that were anesthetized and maintained under physiologic conditions as previously described[20,22]. The swine model was chosen since it has been widely used to study defibrillation due to its anatomy and arrhythmia characteristics[20,22-26]. Experiments were performed in accordance with Institutional Animal Care and Use Committees of the Faculty of Medicine, Chiang Mai University. All animals were housed and maintained in compliance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996). A catheter, with a 34-mm platinum coated titanium coil electrode (Guidant Inc., USA), was inserted into the right ventricular apex. A 68-mm electrode catheter was positioned at the junction between the right atrium and superior vena cava. The position of the catheters was verified with fluoroscopy. The blood pressure, ECG, heart rate, core body temperature, arterial blood gas, plasma O_2 saturation, respiratory rate, and $EtCO_2$ were monitored continuously throughout the entire study.

Defibrillation protocol

Ventricular fibrillation (VF) was induced by 50-Hz alternating current delivered via an electrode at the tip of the right ventricular catheter. After 10 seconds of VF, defibrillation was attempted with biphasic shocks (Ventak, Guidant Inc., USA), with electrodes at the right ventricular apex as a cathode, and at the superior vena cava as an anode for the first phase. A minimum of 4 minutes was allowed to elapse between VF episodes. If the shock failed to defibrillate, a rescue shock (20-30 J) was delivered within 10 sec.

The DFT in each group was determined using a three-reversal up/down protocol[20,27]. Briefly, the initial shock strength was started at 400 V. For a successful defibrillation episode, the leading edge voltage was decreased in 80 V steps per defibrillation attempt until a first reversal from the successful defibrillation to a failed defibrillation episode was achieved. If the initial shock was unsuccessful, the leading edge voltage was increased in 80 V steps per defibrillation attempt until a first reversal from the failed defibrillation to a successful defibrillation episode was achieved. At each reversal point, the algorithm was iterated in the opposite direction. After the first reversal point was obtained, the strength of the voltage step was diminished to 40 V, and 20 V after the second reversal point. The DFT was defined as the lowest energy requirement for successful defibrillation after the three reversal points were obtained, when the next lower setting failed to defibrillate the heart.

Twenty-four pigs were randomly assigned into four groups (Fig. 1). In group 1, the DFT (control-DFT) was determined at the beginning of the study. After the control DFT was obtained, a 50-mg stock solution (0.5 mg/mL) of sildenafil was administered intravenously at the rate of 2 mL/minute over 50 minutes[11]. In group 2, a stock solution of 100-mg of sildenafil (1 mg/mL) was administered at the same rate as that in group 1.To confirm that an increase in plasma volume did not affect the DFT, a similar protocol to the one in group 1 was performed in groups 3 and 4, except for saline (100 mL), which was administered at the same rate as that in group 1. At the end of sildenafil and saline infusion, NTG was administered intravenously in groups 1, 2 and 3 at a rate of 5 □g/min, with an increment of 5 □g/min every 5 minutes. The DFT was determined again after NTG was infused for 20 minutes. The animal was euthanized by VF induction at the end of the study.

Drug administration

Sildenafil (Pfizer) in tablet form (50 and 100-mg) was dissolved in 100 mL of normal saline just before the experiment to form a stock solution. The solution was then filtered, and a clear solution was obtained. Two different concentrations of sildenafil were injected intravenously at the rate of 2 mL/min over 50 minutes. Intravenous administration of 50-mg of sildenafil has been shown to represent ~100-mg of sildenafil citrate taken orally, whereas 100-mg of sildenafil infusion has been shown to be a supra-therapeutic dosage (~ > 200-mg taken orally)[1,11]. In the present study, NTG was used as a nitric oxide donor. NTG (Schwarz/Berli Jucker) at 5 mg (5 mL) was added into 0.9% NaCl 45 mL, forming a stock solution of NTG at 100 □g/mL. NTG was

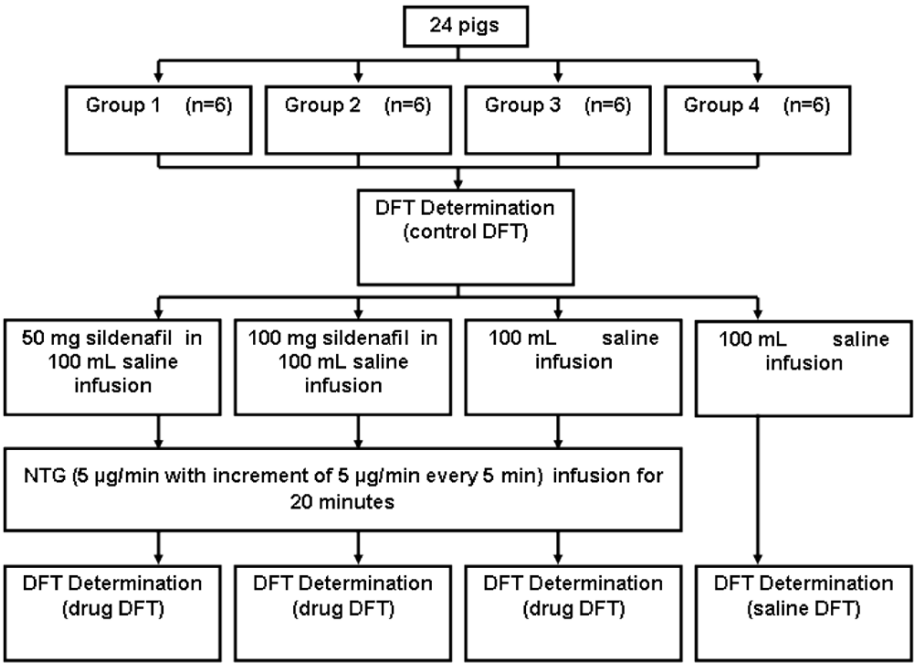

Fig. 1 Illustrated diagram of the study protocol for DFT determination,. pigs were randomly assigned into four groups equally, in each group, the DFT was determined at the beginning of the study and after interventions

administered intravenously at a rate of 5 □g/min, with an increment of 5 □g/min every 5 minutes. The increment was terminated if the systolic blood pressure fell to 20 mmHg below the baseline.

Statistical analysis

Values are expressed as mean ± SD. Comparisons of data between control and drug-DFT within each animal were performed using the student's t-test. A $p < 0.05$ was considered statistically significant.

Results

The average weight of the pigs used in the present study was 26 ± 1 kg. The total number of shocks delivered to each animal was 13 ± 1. The average number of shocks delivered to the animal before obtaining the DFT was 6 ± 1 in the control group and 6 ± 1 in the drug (sildenafil-NTG) or saline (either individually or in combination with NTG) injected groups.

In group 1, the peak voltage and total energy for the control DFT was 404 ± 28 V and 11 ± 2 J, respectively. After 50-mg of sildenafil-NTG infusion, the DFT (402 ± 33 V, 11 ± 2 J, for the peak voltage and total energy respectively) was not different from the control DFT ($p = 0.7$ and $p = 0.9$, respectively, Table 1). Both the impedance and pulse width were not changed after drug administration. The systolic blood pressure after 50-mg of sildenafil-NTG infusion was significantly lower than that in the control ($p < 0.05$, Table 1). However, the heart rate before and after drug administration was not significantly different (Table 1).

In group 2, the peak voltage and total energy for the control DFT was 444 ± 31 V and 14 ± 2 J, respectively. After 100-mg of sildenafil-NTG infusion, the DFT (521 ± 18 V, 19 ± 1 J, for the peak voltage and total energy respectively) was significantly higher than that in the control group (Table 1). The 100-mg of sildenafil-NTG infusion significantly increased the DFT by 17% of the leading-edge voltage and 37% of total energy. No changes in the impedance and pulse width were found in this group. The systolic blood pressure after 100-mg of sildenafil-NTG infusion was significantly lower than that in the control ($p < 0.05$, Table 1). The heart rate before and after drug administration was not different ($p = 0.3$).

In group 3, the peak voltage and total energy for the control DFT was not different from that in the control group (Table 1). The systolic blood pressure after saline-NTG infusion was significantly lower than that in the control group ($p < 0.05$, Table 1). The im-

Table 1. DFT and hemodynamic parameters measured before and after drug (sildenafil-NTG) or saline (either individually or in combination with NTG) administration

Parameters	Group I (n = 6)		Group II (n = 6)		Group III (n = 6)		Group IV (n = 6)	
	Control	50-mg Sildenafil + NTG	Control	100-mg Sildenafil + NTG	Control	100-mL Saline + NTG	Control	100-mL Saline only
Delivered voltage (Volts)	404 ± 28	402 ± 33	444 ± 31	521 ± 18*	424 ± 26	427 ± 34	439 ± 14	417 ± 17
Total energy (Joules)	11 ± 2	11 ± 2	14 ± 2	19 ± 1□	12 ± 2	13 ± 2	14 ± 1	13 ± 1
Impedance (Ohm)	61 ± 2	61 ± 2	60 ± 2	59 ± 3	62 ± 2	62 ± 1	61 ± 3	58 ± 3
Pulse width (msec)	15 ± 1	15 ± 1	15 ± 1	15 ± 1	15 ± 1	15 ± 1	16 ± 1	15 ± 1
Systolic BP (mmHg)	97 ± 3	84 ± 3□	89 ± 4	76 ± 4□	106 ± 3	95 ± 5□	90 ± 3	102 ± 3□
Heart rate (bpm)	88 ± 4	94 ± 5	106 ± 4	95 ± 7	99 ± 4	100 ± 7	106 ± 2	116 ± 6

* $p < 0.004$ compared to control; □ $p < 0.002$ compared to control; □ $p < 0.05$ compared to control

pedance, pulse width, and heart rate before and after drug administration were not different ($p = 0.7$).

In group 4, the peak voltage and total energy for the control DFT was not different from that in the control group (Table 1). The impedance and pulse width were not altered after drug infusion. The systolic blood pressure after saline infusion was significantly higher than that in the control group ($p < 0.05$, Table 1). However, the heart rate before and after drug administration was not different ($p = 0.1$).

Discussion

The findings of the present study could be divided into 2 areas of concern: effects on the DFT and those on blood pressure and heart rate. The major findings were as follows: (1) Intravenous administration of 100-mg of sildenafil-NTG combination (group 2) significantly increased the DFT; (2) Infusion of 50-mg of sildenafil-NTG (group 1) as well as saline either individually (group 4) or in combination with NTG (group 3) did not change the DFT; (3) The administration of 50-mg of sildenafil-NTG (group 1), 100-mg of sildenafil-NTG (group 2), and saline-NTG (group 3) significantly decreased the systolic blood pressure (SBP); and (4) The heart rate was not altered after drug (sildenafil-NTG) and saline (either individually or in combination with NTG) administration.

Sildenafil-NTG combination and defibrillation efficacy

It was shown previously that sildenafil at the supra-therapeutic level in combination with nitric oxide donor promotes fatal arrhythmias[19]. In that study, sildenafil alone was not arrhythmogenic even at a supra-therapeutic concentration, suggesting that nitric oxide may play a role in the arrhythmogenicity of sildenafil. Recently, sildenafil demonstrated an increase in the DFT when a supra-therapeutic dose was given intravenously, but not when the therapeutic dose was administered[20]. However, the effect of the sildenafil-nitric oxide donor combination on defibrillation efficacy has never been investigated. To the best of the authors' knowledge, the present study is the first to investigate the effect of sildenafil-nitric oxide donor on defibrillation efficacy. The present results demonstrated that intravenous administration of 50-mg of sildenafil (i.e. representing the therapeutic plasma level[11]) in combination with NTG does not affect the DFT.

Since the authors' previous study demonstrated that 50-mg of sildenafil alone does not affect the DFT when administered intravenously, the results of the present study indicate no detrimental effect of added NTG on defibrillation efficacy. Furthermore, the present study demonstrated that the combination of 100-mg of sildenafil (i.e. a supra-therapeutic plasma level[11]) and NTG significantly increased the DFT when administered intravenously. It was shown previously that the intravenous administration of 100-mg of sildenafil alone significantly increased the DFT by 19% of voltage and 38% of total energy[20]. In the present study, a combined 100-mg of sildenafil-NTG raised the DFT by 17% of voltage and 37% of total energy. Since the results from using 100-mg of sildenafil alone or 100-mg of sildenafil-NTG combination demonstrated a similar percentage of DFT increment by both voltage and total energy, these findings indicate no beneficial or worsening effect of added NTG on defibrillation efficacy over sildenafil administered in a supra-therapeutic dose.

Many studies have been carried out to validate the cardiac electrophysiological effects of sildenafil[13,14,16,17,28,29]. By using human ether-a-go-go-related gene (HERG)-transfected HEK293 cells, Geelen et al [13] demonstrated that sildenafil at the supra-therapeutic level prolongs cardiac repolarization by blocking the rapid component of the delayed rectifier potassium current (I_{Kr}). Accordingly, sildenafil should be expected to improve defibrillation efficacy by lowering the DFT, as do most other I_{Kr} blockers, such as sotalol and dofetilide[30,31]. However, a recent study performed by Chiang et al [12] showed different findings. They demonstrated that sildenafil at a therapeutic concentration neither blocked I_{Kr} and I_{Ks} in guinea pig ventricular myocytes, nor prolonged cardiac repolarization in guinea pig papillary muscles and canine purkinje fibers. Moreover, they also found that sildenafil at supra-therapeutic concentrations caused shortening of cardiac repolarization, presumably through its blocking effect on $I_{Ca,L}$ [12]. In an in vivo study using a canine model, Sugiyama et al demonstrated that intravenous administration of sildenafil at therapeutic to moderate supratherapeutic concentrations did not affect the action potential duration[14]. Therefore, the definite effect of sildenafil on cardiac ion channels must be investigated further and the discrepancy of results verified. Nevertheless, the authors' previous study[20], and this present study, demonstrated the undesired effect on defibrillation efficacy of the supra-therapeutic plasma level of sildenafil.

In the present study, the increase in the DFT after the combination of 100-mg of sildenafil and NTG administration could be due to its effects on cellular electrophysiological alterations in cardiomyocytes. Sildenafil is known to inhibit PDE-5, causing a net increase in intracellular cGMP concentrations[1,32]. Musialek et al[33] found that an increase in cellular cGMP could stimulate the hyperpolarization-activated inward current (I_f), which may promote an "automatic" tachycardia[33]. However, the constant heart rate after sildenafil administration at both therapeutic and supra-therapeutic concentrations reported in the present study suggests that this mechanism should not be the cause of a high DFT. At supra-therapeutic concentrations, sildenafil blocks $I_{Ca,L}$ and accelerates cardiac repolarization[12], which may possibly lead to a shortening of the action potential duration (APD) and effective refractory period (ERP). These electrophysiological changes could be responsible for an attenuation of defibrillation efficacy, resulting in the increase in the DFT found in the present study. As for the sildenafil-NTG combination, Yoo et al recently reported that sildenafil did not augment NTG to increase the plasma cGMP concentration in dogs[34]. This might explain no augmentative effect of NTG on defibrillation efficacy when given at either 50-mg or 100-mg of sildenafil, as reported in the present study. Further defibrillation studies such as cardiac mapping are necessary to elucidate the mechanism of increased DFT by supra-therapeutic doses of sildenafil.

Conclusion

The intravenous administration of combined 100-mg of sildenafil (i.e. a supra-therapeutic concentration) and NTG significantly increased the DFT (37% total energy). No synergistic effect of NTG was found on the DFT, when administered together with sildenafil. Sildenafil is used increasingly in both ED and pulmonary arterial hypertension, and if this adverse effect is also consistent in humans, the drug should be used with caution in patients with relatively high DFT. Care should be taken when prescribing sildenafil, individually or in combination with nitric oxide donors, to patients with a high DFT at baseline, pulmonary hypertension that requires prolonged use of these drugs, and impaired drug elimination such as hepatic or renal insufficiency.

Study limitations

Although the present study demonstrated an increase in the DFT after intravenous administration of a supra-therapeutic plasma concentration of sildenafil combined with NTG using a standardized swine model of approximate human heart size, the present study was performed in normal pig hearts and results may differ in diseased hearts. Moreover, the pharmacokinetics and metabolism of these drugs vary substantially between species, therefore the results could be similar or different in humans. Although the effective refractory period was not measured in the present study, it was shown in the introduction of the present study that intravenous administration of sildenafil at the sub- to supra-therapeutic level did not affect either monophasic action potential duration or effective refractory period. Defibrillation studies at cellular and molecular levels are needed to verify the mechanistic insight by which sildenafil increases the DFT.

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ผลของการให้ยา sildenafil ร่วมกับ nitric oxide donor ต่อประสิทธิภาพในการทำ defibrillation

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การศึกษาก่อนหน้านี้พบว่าการให้ยา sildenafil ในระดับสูงว่าระดับที่ใช้ในการรักษา ทำให้ประสิทธิภาพในการทำ defilbrillation ลดลง อย่างไรก็ตามผลของการให้ยา sildenafil ร่วมกับ nitroglycerine (NTG) ต่อประสิทธิภาพการทำ defibrillation ยังไม่มีการศึกษา งานวิจัยนี้ศึกษาว่าผลของยา sildenafil ในระดับปกติที่ใช้ในการรักษา เมื่อให้รวมกับ nitroglycerine จะมีผลต่อประสิทธิภาพในการทำ defibrillation หรือไม่ การศึกษานี้ใช้สุกร 24 ตัว (20 -25 กิโลกรัม) โดยทำการวัด defibrillation threshold (DFT) หลังจากนั้นแบ่งสุกรเป็น 4 กลุ่ม โดยที่กลุ่มที่ 1 ได้รับสารละลายที่มียา sildenafil อยู่ 50 มิลลิกรัม (ระดับ therapeutic), กลุ่มที่ 2 ได้รับสารละลายที่มียา sildenafil 100 มิลลิกรัม (ระดับสูงกว่า therapeutic), กลุ่มที่ 3 และ 4 ได้รับน้ำเกลือ 100 มิลลิลิตรเข้าทางหลอดเลือดด้วยอัตราเร็ว 2 มิลลิลิตรต่อนาที จากนั้น NTG จะถูกให้ทางเส้นเลือดดำในกลุ่มที่ 1-3 ด้วยอัตรา 5 ไมโครกรัมต่อนาที โดยเพิ่มขนาดของ NTG 5 ไมโครกรัมต่อนาที ทุก ๆ 5 นาที จากนั้น DFT จะถูกวัดอีกครั้งหนึ่งหลังได้ NTG ไปแล้ว 20 นาที ผลการศึกษาพบว่าในกลุ่มที่ 1 นั้นค่า DFT หลังได้รับยาไม่แตกต่างจากค่า DFT ตอนเริ่มต้น ในกลุ่มที่ 2 พบว่าค่า DFT หลังได้รับยามีค่าสูงขึ้นกว่าค่า DFT ตั้งต้น ในกลุ่มที่ 3 และ 4 นั้น ค่า DFT ทั้ง 2 ไม่มีความแตกต่างกัน ดังนั้นจึงสรุปได้ว่า ยา sildenafil ที่ระดับ supratherapeutic ร่วมกับ NTG เพิ่มค่า DFT อย่างมีนัยสำคัญ ซึ่งผลต่อค่า DFT นี้นั้น น่าจะเกิดมาจากผลของ sildenafil ไม่ใช่มาจาก NTG