

3-1-2012

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Recommended Citation

Maneesang, W; Verachai, V; and Kalayasiri, R. (2012) "Effects of video cues on inhalants craving in individuals receiving inhalants substance-dependency treatment," *Chulalongkorn Medical Journal*: Vol. 56: Iss. 2, Article 3.

DOI: <https://doi.org/10.58837/CHULA.CMJ.56.2.3>

Available at: <https://digital.car.chula.ac.th/clmjournal/vol56/iss2/3>

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Effects of video cues on inhalants craving in individuals receiving inhalants substance-dependency treatment

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Maneesang W, Verachai V, Kalayasiri R. Effects of video cues on inhalants craving in individuals receiving inhalants substance-dependency treatment. Chula Med J 2012 Mar - Apr; 56(2): 147 - 61

Background : *Subjective craving, a desire to take a substance, occurs when individuals with substance dependence are exposed to specific cues. However, effects of cue exposure on inhalant craving have not been studied.*

Objective : *The objective of this study is to study craving responses when individuals who are receiving inhalant dependency treatment at Thanyarak Institute are watching inhalant video cues.*

Method : *Subjective inhalant craving responses of the thirty-four male inhalant dependent patients were measured by the modified version of Penn Alcohol Craving Scale for Inhalants (PACS-inhalants) and the Visual Analog Scale (VAS). The instruments were shown every five minutes on a computer screen before the test and right after exposure of each of the three sets of silent video cues for inhalants (one-minute length per set of video cues) and each of the three sets of neutral video every five minutes (one-minute length per set of neutral video). Levels of systolic and diastolic blood pressures and pulse rate were also measured. Data were analyzed using repeated measure ANOVA. Scores on PACS-inhalant and VAS were also tested for correlation using Pearson's correlation test.*

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Results : Craving responses as measured by PACS-inhalants and VAS were at high correlation (Pearson correlation = 0.83, $p < 0.001$). The effects of time on craving responses during exposure to inhalant video cues were observed (PACS-inhalants; $p < 0.001$, $F_{3.1, 102.2} = 19.7$) (VAS-craving; $p < 0.001$, $F_{5.0, 164.3} = 5.7$). Post-hoc analysis of PACS-inhalants and VAS showed differences of craving responses at the times between cue and neutral videos (cues > neutral videos). However, there were differences of craving at the times between pre-test and cue exposure only when craving was measured by PACS-inhalants (cues > pre-test), but not by VAS. In addition, the effects of inhalant cues on systolic blood pressure were observed when the blood pressures are compared during cue exposure with neutral video, but not with the pre-test.

Conclusions : Our findings show evidence of the effect of exposure to inhalant video cues on increasing of subjective craving response. Although non-clinically significant, a statistically significant difference between exposure to video cues and neutral videos were observed.

Keywords : Video, cue, inhalant, craving.

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Received for publication. April 10, 2011.

วรรณจรี มณีแสง, วิโรจน์ วีระชัย, รัศมน กัลยาศิริ. ผลของการใช้วิธีทัศนกระตุ้นความอยากเสพยาในผู้เข้ารับการบำบัดการติดยาเสพติด. จุฬาลงกรณ์เวชสาร 2555 มี.ค. -เม.ย.; 56(2): 147 - 61

- เหตุผลของการทำวิจัย** : ผู้ติดยาเสพติดเกิดความอยากเสพยาได้เมื่อได้รับสิ่งเร้าในการกระตุ้น อย่างไรก็ตาม ยังไม่เคยมีการทดลองการกระตุ้นความอยากเสพยาในผู้ติดยาเสพติดมาก่อน
- วัตถุประสงค์** : เพื่อศึกษาผลการเปลี่ยนแปลงของความอยากเสพยาในผู้เข้ารับการบำบัดการติดยาเสพติด ณ สถาบันธัญญารักษ์ ได้รับสิ่งเร้าเป็นวิธีทัศนกระตุ้นความอยากเสพยา
- วิธีการศึกษา** : เก็บรวบรวมข้อมูลจากชายไทย 34 คน ที่มาเข้ารับการบำบัดการติดยาเสพติด ณ สถาบันธัญญารักษ์ โดยใช้แบบประเมินแบบตอบด้วยตนเองบนหน้าจอคอมพิวเตอร์ ซึ่งประกอบด้วย แบบประเมินความอยากเสพยาในผู้ติดยาเสพติดที่ดัดแปลงจาก Penn Alcohol Craving Scale (PACS-inhalants) และแบบประเมินความรู้สึก Visual Analog Scale (VAS) เมื่อก่อนทำการทดลอง ระหว่างการทดลองและหลังการทดลอง โดยการทดลองนี้จะให้กลุ่มตัวอย่างรับชมวิธีทัศนที่มีความยาวครั้งละ 1 นาที ซึ่งเป็นภาพกระตุ้นความอยากเสพยาในผู้ติดยาเสพติดจำนวน 3 ครั้ง และเป็นภาพธรรมชาติต่ออีกจำนวน 3 ครั้ง ระยะห่างระหว่างครั้งทุก 5 นาที และแบบประเมินจะปรากฏขึ้นบนหน้าจอคอมพิวเตอร์หลังภาพกระตุ้นและภาพธรรมชาติในแต่ละครั้ง เพื่อให้กลุ่มตัวอย่างสามารถเลือกคำตอบผ่านหน้าจอคอมพิวเตอร์ โดยจะมีการวัดระดับสัญญาณชีพ (ความดันโลหิตและชีพจร) ของกลุ่มตัวอย่างด้วยเครื่องวัดอัตโนมัติ จากนั้น นำข้อมูลที่บันทึกได้มาวิเคราะห์ด้วยสถิติ repeated measure ANOVA และ หาค่าความสัมพันธ์ของแบบประเมินทั้งสองด้วยค่าการทดสอบของ Pearson's correlation

- ผลการศึกษา :** พบว่าแบบประเมินทั้งสองมีค่าความสอดคล้องกันในระดับสูงอย่างมีนัยสำคัญทางสถิติ (*Pearson correlation* = 0.83, $p < 0.001$) และพบว่าการดูวิดีโอทัศน์ในแต่ละครั้งเมื่อเวลาผ่านไปมีผลต่อคะแนนความอยากเสพสารระเหยที่แตกต่างกัน (*PACS-inhalants*; $p < 0.001$, $F_{3.1, 102.2} = 19.7$) และ (*VAS-craving*; $p < 0.001$, $F_{5.0, 164.3} = 5.7$) โดยคะแนนความอยากเสพสารระเหยเมื่อใช้วิดีโอทัศน์กระตุ้นมีระดับคะแนนมากกว่าการดูวิดีโอทัศน์ธรรมชาติอย่างมีนัยสำคัญทางสถิติ จากการประเมินโดยใช้แบบประเมิน *PACS-inhalants* และ แบบประเมิน *VAS* อย่างไรก็ตาม การดูวิดีโอทัศน์กระตุ้นมีผลต่อคะแนนความอยากเสพสารระเหยมากกว่าคะแนนก่อนการทดลองอย่างมีนัยสำคัญทางสถิติ จากการใช้แบบประเมิน *PACS-inhalants* เท่านั้น โดยไม่พบความแตกต่างนี้จากการใช้แบบประเมิน *VAS* นอกจากนี้ การดูวิดีโอทัศน์กระตุ้นมีผลต่อระดับความดันโลหิต *systolic blood pressure* แตกต่างจากการดูวิดีโอทัศน์ธรรมชาติอย่างมีนัยสำคัญทางสถิติ แต่ไม่พบความแตกต่างทางสถิติของระดับความดันโลหิต *systolic blood pressure* นี้ขณะที่ดูวิดีโอทัศน์กระตุ้น เมื่อเทียบกับก่อนการทดลอง
- สรุป :** การใช้สิ่งเร้าที่เป็นภาพวิดีโอกระตุ้นความอยากเสพสารระเหยมีผลเพิ่มความอยากเสพสารระเหย นอกจากนี้ระดับความดันโลหิตของกลุ่มตัวอย่างมีความแตกต่างกันทางสถิติ ขณะดูวิดีโอทัศน์กระตุ้นความอยากเสพ เมื่อเทียบกับขณะดูวิดีโอทัศน์ภาพธรรมชาติ ทั้งนี้ ไม่พบว่ามีผลทางคลินิกจากการเปลี่ยนแปลงของความดันโลหิตดังกล่าว
- คำสำคัญ :** วิดีทัศน์, ตัวกระตุ้น, สารระเหย, ความอยากเสพสาร.

Craving, “the conscious experience of a desire to take a drug or substance”, is a target symptom for pharmacotherapy of substance dependence.⁽¹⁾ The urge to take drugs due to experiencing craving is considered a sign for psychological withdrawal symptom⁽²⁾, a manifestation for substance dependence.^(3, 4) Craving varies, depending on classes of substance of abuse from substances that produce strong (i.e., cocaine, heroin, cigarette, methamphetamine)^(4 - 6) to mild level of craving (i.e., caffeine).⁽⁷⁾ Volatile substances or inhalants are neurotoxic substances that have been abused worldwide but little is known on their craving effect. To our knowledge, there were case series (N = 3 to 17)⁽⁸⁾ that mentioned inhalant craving in the context of inhalant withdrawal symptoms.⁽⁹⁾

Little is known about the symptoms of inhalant dependence⁽¹⁰⁾, despite increasing prevalence of inhalant used in Thailand⁽¹¹⁾ and around the world⁽¹²⁾ ranking inhalant as the second most common substance of abuse in the US.⁽¹³⁾ Inhalant use is associated with social problems including crime and violence^(14, 15) and medical (i.e., allergy⁽¹⁶⁻¹⁸⁾, neurocognitive impairment⁽¹⁹⁾ and mental health (i.e., depression⁽²⁰⁾, psychosis⁽²¹⁾). Inhalants which are commonly abused comprise of many chemicals that are used in commercial industry, including toluene or xylene in glue, lacquer, thinner, or acetone in nail polish remover.⁽²²⁾ In Thailand, inhalants were first reported as a drug of abuse in 1977, and has been widely used by youngsters because the chemicals are available in industries and they are inexpensive.⁽¹¹⁾ In 1996, the Thailand Development Research Institute (TDRI) reported that inhalants were in the top five substances of abuse in Thailand.⁽¹¹⁾

Subjective craving may occur during exposure to specific environment or “cue exposure” based on conditioning learning theory.^(23 - 26) For example, watching video cues of cocaine stimulates the feeling of drug need, rising of heart rate, and blood pressure.^(27, 28) Effects of video cues on inhalant craving may be used as a tool to investigate efficacy of therapy on reducing craving response during cue exposure and ultimately on inhalant dependency treatment.

Methods

Subjects

Data on the screening day of cue-induced craving of thirty-four Thai-speaking male subjects participating in a study to investigate the efficacy of a treatment in reducing cue-induced inhalant craving were used in this study. Sample size was calculated based on cross - over experimental designs of the parent study. Drop out during the experiment was expected at 10%. The researcher thus determined the sample of 17 persons for the total of 2 groups, totally 34 persons were recruited (manuscript in preparation).

All subjects aged ≥ 18 years, met the Diagnostic and Statistical Manuals for Mental Disorders version IV (DSM-IV)^(15, 29, 30) criteria for inhalant dependence by using the Mini International Neuropsychiatric Interview (M.I.N.I – lifetime, computerized Thai version)^(31 - 33), and received inpatient inhalant dependency treatment at Thanyarak Institute on Drug Abuse between July and November 2010. Individuals with current major psychiatric disorders (e.g., psychotic disorder, major depressive disorder), other illicit substance dependence, or chronic medical diseases and/or were receiving any

pharmacological treatment were excluded from the study. Sections A (Demographic Information) and B (Medical History) of the Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA), computerized Thai version^(30, 34, 35) were also used in the study for the above exclusion criteria. Before recruitment, all participants had to give their written informed consent. The study protocol has been approved by the Ethics Committees of the Faculty of Medicine, Chulalongkorn University and Thanyarak Institute on Drug Abuse.

Materials

Materials used in this study had two parts:

1. Measurements for inhalant craving:

Craving responses to inhalant of the subjects were measured by two instruments: the modified version of Penn Alcohol Craving Scale (PACS)⁽³⁶⁾ and the Visual Analog Scale (VAS). PACS comprises of five questions, each of which has seven possible responses, scored from 0 to 6. Higher scores of PACS mean high craving responses. The instrument was translated into Thai with the replacement of the word “alcohol” with “inhalants”, with additional modification to measure inhalant “current” craving (unlike parent version that referred to “prior one-week”) making the Thai version of PACS-inhalants. The Thai version of PACS-inhalants was tested for content validity by three Thai/English-speaking psychiatrists and was back-translated into English for correctness of the content. Parent English version of PACS has high reliability (Cronbach’s alpha = 0.92) for alcohol craving.^(37, 38) The Thai version of PACS-inhalants was also tested

for reliability in thirty patients with inhalant dependence at the outpatient clinic of Thanyarak, and had a high reliability score (Cronbach’s alpha = 0.81). The Thai PACS-inhalants was transformed into an electronic program that the subjects could respond independently on the computer screen. In addition to the PACS-inhalants that was used to measure craving response, the VAS, which is a zero-to-ten scale measuring subjective feelings (0 = not at all; 10 = most ever) was used in this study. Subjects independently scored their level of craving for inhalant by using a mouse clicking on a line with ten-centimeter length on computer screen.⁽³⁹⁾ The only computer skill to do the test was the skill of mouse using (i.e., no typing skills or any other computer program skills were required in order to be able to do the test). The subjects had tried the test on the screening day. No subject was found to be unable to use the mouse.

2. Inhalants video cue:

The subjects were exposed to silent video cues with one-minute length every five minutes for three times. The selected contents in the video cues were a combination of twelve pictures of various kinds of commonly abused inhalants and their uses.⁽⁴⁰⁾ The pictures were displayed at 5 seconds per picture. After watching the three sets of inhalants video cue, the subjects were exposed to sets of neutral pictures (e.g., forest, water fall, river, and ocean) every five minutes for three times. An investigator (WM) was present at all time to observe subjects’ attention to the video cues and neutral pictures, but she was not allowed to talk to the subjects during the subjects’ exposure to the video cue and neutral video.

PACS-inhalants and VAS were applied at five-minutes before the test and after exposure to each of the sets of inhalant video cues and neutral videos (i.e., every five minutes) and five-minutes after the test. Levels of systolic and diastolic blood pressures and pulse rate were also measured.

Data Analysis

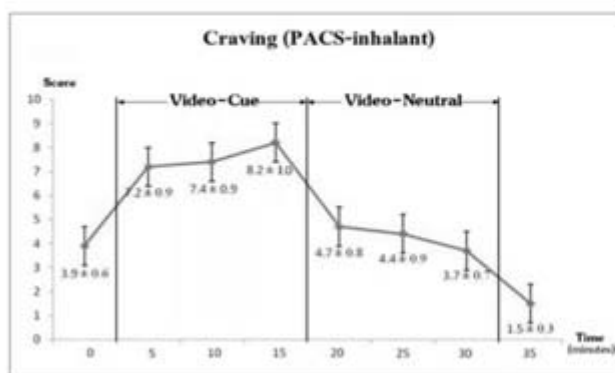
Craving responses and vitals were tested by visual inspection. Normally distributed data of the levels of inhalant craving from VAS and PACS-inhalants, systolic and diastolic blood pressures, and pulse rate before and during watching video cues (e.g., pre-test, cue-1, cue-2, cue-3) and during and after watching neutral video (e.g., neutral-1, neutral-2, neutral-3, post-test) were analyzed using repeated measure ANOVA. Scores on VAS-craving and PACS-

inhalant were also tested for correlation using Pearson's correlation.

Results

The mean age of subjects was 27.9 ± 1.4 years. The subjects had averaged years of education at 7.2 ± 0.6 years. Most subjects had single marital status ($n = 25$; 73.5%) and 22 (64.7%) subjects had family with the total income of less than 15,000 baht/month (1U.S.\$ = 30 baht). Glue was an inhalant of choice in 32 subjects (94.1%) and thinner was abused by the rest (5.9%). Averaged time of using inhalants was 5.8 ± 1.1 years. The prevalences of other substance use in this cohort were as follow; cigarette ($n = 22$, 64.7%), alcohol ($n = 20$, 58.8%), methamphetamine ($n = 20$, 58.8%), marijuana ($n = 13$, 38.2%), and opioids ($n = 5$, 14.7%), respectively.

A.



B.

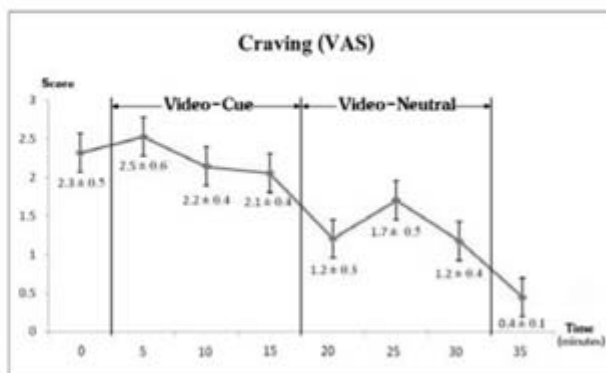


Figure 1. Illustrations of cue-induced inhalant craving response measured by Penn Alcohol Craving Scale for inhalants (PACS-inhalants) (Figure 1A) and Visual Analog Scale (VAS-craving) (Figure 1B) of 34 subjects with inhalant dependence. There is a significant effect of time on inhalant craving from the two measurements (PACS-inhalants; $p < 0.001$, $F_{3.1, 102.2} = 19.7$) (VAS-craving; $p < 0.001$, $F_{5.0, 164.3} = 5.7$).

Figure 1 shows graphical craving responses at pretest (0-min), cue-1 (5-min), cue-2 (10-min), cue-3 (15-min), neutral-1 (20-min), neutral-2 (25-min), neutral-3 (30-min), and post-test (35-min), respectively. The significant effect of time on inhalant craving was observed from the two measurements (PACS-inhalants; $p < 0.001$, $F_{3.1, 102.2} = 19.7$) (VAS-craving; $p < 0.001$, $F_{5.0, 164.3} = 5.7$).

Post-hoc analysis of PACS-inhalants revealed that the effect of time was attributed to differences of levels of craving between: 1) pre-test and cue-1, cue-2, cue-3, post-test (mean differences = 3.3, 3.5, 4.2, -2.4; $p < 0.001$); 2) cue-1 and neutral-1, neutral-2, neutral-3, post-test (mean differences = -2.5, -2.7, -3.4, -5.7; $p < 0.005$); 3) cue-2 and neutral-1, neutral-2, neutral-3, post-test (mean differences = -2.7, -2.9, -3.7, -5.9; $p < 0.005$); and, 4) cue-3 and neutral-1, neutral-2, neutral-3, post-test (mean differences = -3.5, -3.7, -4.4, -6.6; $p < 0.001$). However, post-hoc analysis of VAS-craving showed no difference of craving responses between pre-test and any of the cue exposure. On the contrary, the effect of time on VAS-craving was attributed to the differences of VAS-craving between pre-test or cue exposure and neutral video ($p < 0.005$). Specifically, the levels of VAS-craving during watching the neutral video were lower than those during watching the inhalant cues or the pre-test. The mean craving responses as measured by PACS-inhalants and VAS-craving were excellently correlated (Pearson correlation = 0.83, $p < 0.001$).

Objective responses when watching the inhalant cues were measured. The significant effect of time on systolic blood pressure was observed ($p = 0.008$, $F_{4.8, 159.0} = 3.3$). Post-hoc analysis

suggested that the effect of time was because of the differences of systolic blood pressure between cue-1/neutral-1 (mean difference = -2.2, $p = 0.02$), cue-1/neutral-3 (mean difference = -4.0, $p = 0.007$), cue-2/neutral-2 (mean difference = -1.7, $p = 0.025$), cue-2/neutral-3 (mean difference = -3.3, $p = 0.009$), cue-3/neutral-1 (mean difference = -3.0, $p = 0.03$), cue-3/neutral-2 (mean difference = -3.2, $p = 0.001$), cue-3/neutral-3 (mean difference = -4.8, $p = 0.002$), cue-3/post-test (mean difference = -2.6, $p = 0.012$). In contrast, there was no effects of time on diastolic blood pressure ($p = 0.15$, $F_{3.1, 103.0} = 1.8$) or pulse rate ($p = 0.50$, $F_{6.2, 204.2} = 0.9$) (Figure 2).

Discussion

Subjective craving usually occurs for objects or activities associated with pleasurable effects.⁽⁴¹⁾ Craving for a drug is one of the characteristic symptoms for the drug to be considered as addictive substance.⁽⁴²⁾ Previous studies suggested that amygdala and anterior cingulate were responsible for craving response since activations of these brain areas were observed when cocaine dependent subjects were exposed to cocaine video and the activations were associated with cocaine craving response.^(8, 27, 43) Cue-induced craving effects were used widely to investigate treatments for substance dependence.⁽⁴⁴⁾

We found the effect of watching the video cues on inhalant craving compared to the level of craving at baseline (pre-test) which is consistent with previous reports on alcohol^(23, 24), cocaine^(8, 27, 43), nicotine^(44, 45), methamphetamine⁽⁴⁶⁾, and heroin.⁽²⁸⁾ The effect has been observed since the first exposure to video cues (cue-1) and continued until

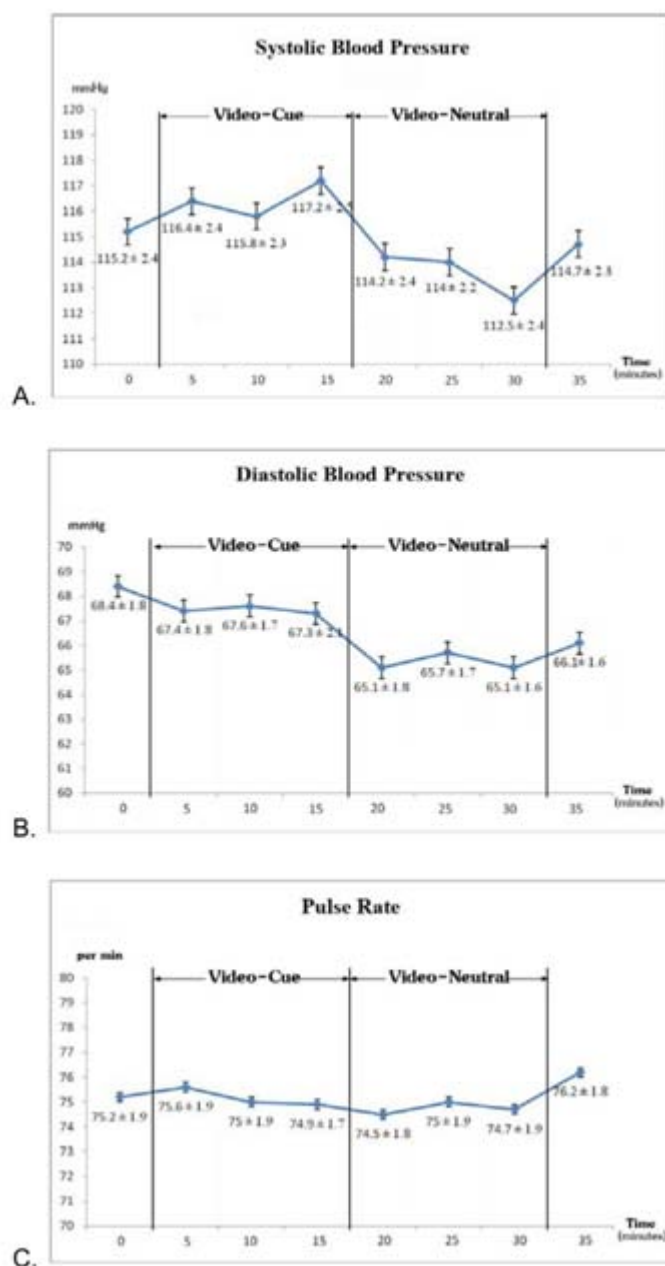


Figure 2. Illustrations of systolic blood pressure (Figure 2A), diastolic blood pressure (Figure 2B) and pulse rate (Figure 3A) measured when the 34 subjects with inhalant dependence were watching the inhalant video cues and neutral videos). There is a significant effect of time on systolic blood pressure ($p = 0.008$, $F_{4.8, 159.0} = 3.3$), but not on diastolic blood pressure ($p = 0.15$, $F_{3.1, 103.0} = 1.8$) or pulse rate ($p = 0.50$, $F_{6.2, 204.2} = 0.9$).

the last exposure (cue-3). Cue may attenuate craving response when subjects are repeatedly exposed for a long period which may be described by learning theory, and it is used in the exposure therapy to reduce fear of specific objects^(47, 48) or

in response prevention (i.e., prevent the response of compulsive behaviors) in obsessive-compulsive disorder (OCD)^(49, 50) resulting in the extinction of the response.⁽⁵¹⁾ In our study, the subjects were only briefly exposed to cue (i.e., one minute exposure for

three times) therefore the extinction of the feelings during cue exposure would not be the case. On the contrary, we did not observe any increase of the craving response when subjects were repeatedly exposed to the inhalant cue for three times. Thus, it might be useful to investigate the effect of inhalant cues for a longer period to see the trend of the effect after repeatedly exposures to inhalant cues.

We observed the effect of video cues on craving response by using PACS-inhalant (Cronbach's $\alpha = 0.81$) but not in the other measurement, VAS (Cronbach's $\alpha = 0.69$). Although the inter-instrument reliability was high between the two measurements, we suspected that the inconsistency of the effect of inhalant cues on craving from the two measurements might be due to the differences in sensitivity/specificity of each measurement. Whereas PACS-inhalant is the instrument with the score derived from the sum of score of five questions; the VAS is only the single digit score that subjectively reports of the feeling based on one question. Likewise, mean systolic blood pressures when watching the video cues were higher than baseline, the effect was not statistically or clinically significant, which is inconsistent with previous studies in cue-induced vital sign change.^(28, 43, 46) We speculated that the negative result on this objective response might be due to the small sample size. However, we observed that the systolic blood pressure and craving response reduced significantly when the subjects were exposed to neutral video, and this reducing effect remained until the end of the study when compared to the baseline (pre-test). We used neutral video to calm down any of the craving or aversive effects from

inhalant video cue that might occur^(45, 46), but the picture we chose might have additive relaxation effect. The result is consistent to a previous study that pictures of nature may have relaxation effects⁽⁵²⁻⁵⁴⁾ as we used the pictures in the biofeedback therapy or to reduce blood pressure.⁽⁴⁶⁾ We suggest that future studies may not use any of the relaxing picture or any intervention to deal with the effect of video cue in order to test the course of craving / vitals effect of inhalant cues and to test whether the craving effect from video cues might be spontaneously attenuated. A previous study, even with stronger substances (e.g. methamphetamine) showed that the craving effect spontaneously reduced without any intervention.⁽⁴⁶⁾

The study had several limitation. Although the largest sample size of its kind, larger sample size is recommended to enhance the reliability of the result and to encourage the result to be more explicit. Second, female was not included in the study since patients receiving inhalant-dependency treatment at the treatment center during the time of investigation were all male. Previous study found that arousing response to visual cocaine cues in female was higher than male⁽⁵⁵⁾, therefore our results that we studied inhalant craving response only in male should be used with caution in the other sex. Likewise, the study was performed at a large substance dependency treatment center, results should be used with caution in general population. Finally, although the PACS-inhalant and VAS were in high correlation, the VAS was a crude scale using only single digit (see discussion above) and needed more description of the craving for the subjects to be able to understand it in the same way.

The findings of this study support the hypothesis that craving for inhalants occurs when inhalant dependent subjects have seen cues of inhalants. One way to help the inhalant dependent patients to reduce craving for the substance may be done by avoiding any exposure to inhalant cues (i.e., pictures). We also successfully created an investigation tool that may be used to investigate the effect of pharmacotherapy or treatment on the reduction of cue-induced inhalant craving. In addition, we also found that pictures of natural landscape may help decrease substance craving and should be encouraged to use in the surroundings of individuals with inhalant dependence.

Acknowledgements

We thank all participants of this study, as well as the staff of Thanyarak Institute for facilitating the process of the study. Also, we would like to thank Chaichana Nimnuan, MD, PhD and Chutima Roomruangwong, MD for helping with the English-Thai translation. We feel grateful to Supakon Wattanasuk for providing technical supports for the computerized versions of the instruments used in the study. Graphics used in the video cues were supported by Sahamongkol Film International Company Limited. This study was partly granted by Chulalongkorn University (the Graduate School Thesis Grant 2554).

R.K. was supported research career by a co-funded grant between TRF/CHE/Chulalongkorn University (RMU5380025;) and Ratchadapisek-sompotch Fund, Chulalongkorn University 2553 (RD/42/53/30).

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