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| **IRB Number:** | **04-1677** | **Legacy ID:** | GCRC-2067 |
| **PI:** | Robert Devlin | **IRB:** | Biomedical |
| **Sponsor:** | US EPA | | |
| **Study Title:** | Physiological Changes in Adults with Metabolic Syndrome Exposed to Concentrated Ultrafine Chapel Hill Air Particles | | |

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| **Certified:** | 10/20/2010 |
| **Reference ID:** | 1962 |

## >> Brief Description of Event

### Subject experienced tachycardia and atrial fibrillation while engaged in a study in the Human Studies Facility

**A1) Did this event occur at a site for which a UNC-CH IRB has direct oversight responsibility or involve a research participant at one of those sites?** **Yes**

**A2) Was the event unexpected in nature, severity, or frequency?** **Yes**

**Please explain:**

**The occurance of ectopic beats in this study population is not unexpected; indeed we have excluded a handful of subjects from other studies because we observed abnormal ECG events in those subjects. However, it was the severity of the events experienced by this individual that has led us to report this as an adverse event. This subject reported no change in her medical history when she was given a physical examination prior to entrance into this study, and all clinical values met inclusion criteria for the study.**

**A3) Do you think the event was related or possibly related to this research?** **Yes**

**Please explain:**

**We cannot completely exlcude the possiblity that this event was related to the subject's participation in the study. However, as, detailed in the response below, the subject participated in a nearly identical EPA study two years ago without incident.**

**A4) Does the event suggest that the research places subjects or others at a greater risk or harm than was previously known or recognized?**

**Economic:** **No**
**Legal:** **No**
**Physical:** **Don't Know**
**Psychological:** **No**
**Social:** **No**

**Please explain all "yes" or "don't know" responses**

**Two years ago, the subject participated in a nearly identical study at the Humans Studies Facility in which she was exposed to air pollution particles. All clinical responses (including ECG) were within the expected range. Prior to enrollment in this study, the subject was given a physical examination and the ECG was normal. Follwoing the incident on October 7, 7he subject was admitted to the UNC hospital overnight for observation, and no abnormalities were observed in her ECG. An echocardiogram was also preformed and showed no abnormalities. EPA medical personnel have followed up with the subject over the weekend and on Monday morning. The subject reports no ill effects and has carried on her daily activities as normal. This incident has made the subject aware that she may be at risk for cardiac events and she plans to follow up with a physican to help reduce risk factors for CV disease.**

## >> Information About the Event

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| **B1) Date of Event:** | **10/07/10** |
| **B2) Location of Event:** | **EPA Human Studies Facility** |

B3) Full Description of Event.

The volunteer was a 58 year old woman with a previous history of volunteering for EPA sponsored health effects studies without incident (subject XCE-227). She reported to the Human Study Facility (HSF) on 10-7-2010 to participate in the first of two exposure sessions for IRB#04-1677. The volunteer had previously undergone the same exposures for this protocol two years ago without incident. The study progressed as expected and the volunteer entered the exposure chamber at 11:21AM. ECG and oxygen saturation were being monitored during the chamber exposure and were normal and consistent. Twenty three minutes into the scheduled two hour exposure to ambient air pollution particles automatic alarms sounded at the chamber consol and the medical station and an automatic ECG printout of an event was printed in the medical station. The subject's ECG reading indicated a 22 beat arrhythmia lasting 10.5 seconds (124bpm). After 10 seconds the subject's heart rate and rhythm were normal and all other vitals remained normal, and the subject reported she was feeling fine. The study nurse, Maryann Bassett, consulted with the on-call doctor, Terry Noah(UNC) and an EPA physician, Dr. Andy Ghio and the decision was made to remove the subject from the chamber. The subject was calmly informed the exposure would be ending and the subject was taken to the HSF medical station for observation. In addition to telemetered ECG leads, the subject was wearing an ambulatory ECG monitor (Holter monitor) to scientifically assess changes in heart rate variability associated with exposure to air pollution particles. Ms. Bassett removed the subject's ambulatory ECG (holter) monitor to review her heart rhythm prior to and during the exposure (the subject's ECG continued to be monitored by telemetry). Readings from the Holter monitor indicated that the subject had two events of atrial premature beats (APBs) - a 3 beat event of 133bpm and a 9 beat event of 135 bpm) while in transit from the HSF to the UNC hospital complex where brachial artery ultrasound measurements were taken as one of the study end points. After evaluation of the subject, Dr. Ghio made an appointment for the subject to be seen at the UNC Cardiology Facility the next day, Friday 10-8-2010. The subject was informed that while these arrhythmias were not an indication of eminent danger, it did indicate there may be an underlying issue that should be examined by a cardiologist soon. While still under observation, the subject's heart rhythm changed and went into atrial flutter followed several minutes later by atrial fibrillation. Upon observing these events the medical station nurses and physicians decided that the subject should be transferred to the ER to be monitored in a hospital setting. It was determined that the safest route would be for her to be transported by EMT. The subject still reported feeling physically fine and agreed to the assessment by Drs. Ghio and Carraway that she should be transported to the ER. Ms. Bassett called 911 and informed the Orange County EMS of the situation. The EMTs arrived within about 5 min began to monitor the subject with their own ECG equipment. The subject's ECG reverted back to normal sinus rhythm prior to transporation to the ER. The subject was hospitalized overnight with remote monitoring for observation. No ECG abnormalities were observed during this time. A cardiologist examined the subject and indicated to the subject that he did not see any findings of concern. An echocardiogram was preformed prior to discharge and the findings were normal. The subject has been scheduled for a cardiac stress test. Ms. Bassett spoke with the subject the following day, Friday 10-8-2010 and throughout the weekend. The subject had resumed her normal daily activities and experienced no symptoms or ill effects. The subject was very thankful for the safety measures that were taken at the EPA. There are no long term consequences of this specific event but it was important for the subject to learn that she is likely at increased risk for future cardiac atrial events and can take necessary steps to reduce her risk.

The following are the notes from Dr. Wayne Cascio, a cardiologist who is also a co-PI on the study, and who examined the ECG readout: 10/07/2010 Time 11:37:34 Frequent APBs and one 7.5 second burst of supraventricular tachycardia. The rhythm is difficult to interpret as a full disclosure print-out but appears to be atrial fibrillation.

10/07/2010 Time: 11:44:40 Atrial fibrillation and flutter converts to sinus bradycardia before reverting to atrial fibrillation.

10/07/2010 Time: 11:44:47 Atrial flutter with 2:1 AV conduction. Mean heart rate 129 bpm. Atrial basic cycle length 240 ms corresponding to an atrial rate of 250 bpm. This rhythm appears to transition to atrial fibrillation that terminates leaving the heart in a sinus bradycardia.

10/07/2010 Time 01:49:xx Probably slow atrial flutter with 2:1 AV conduction with mean rate of 120 bpm. Over the next few seconds the rhythm transitions to atrial fibrillation.

10/07/2010 Time: 01:56:01 Atrial fibrillation with mean rate of 87 bpm. QRS 82 ms, QT 376 ms, QTc 452 ms. Non-specific T wave abnormalities in the inferior leads secondary to atrial fibrillation. Atrial electrical activity is coarse. There are no ST-T wave changes suggestive of ischemia. QTc is 462 ms and QRS duration is normal.

10/07/2010 Time: 01:56:57 Atrial fibrillation with mean rate of 81 bpm. Atrial electrical activity is coarse. There are no ST-T wave changes suggestive of ischemia. QTc is 462 ms and QRS duration is normal.

10/07/2010 Time: 01:57:09 Atrial fibrillation with mean rate of 78 bpm. Atrial electrical activity is coarse. There are no ST-T wave changes suggestive of ischemia. QTc is 462 ms and QRS duration is normal.

10/07/2010 Time: 01:57:20 Atrial fibrillation with mean rate of 80 bpm. Atrial electrical activity is coarse. There are no ST-T wave changes suggestive of ischemia. QTc is 462 ms and QRS duration is normal.

10/07/2010 Time: 02:05:25 Atrial fibrillation with mean rate of 91 bpm. QRS 82 ms, QT 388 ms, QTc 477 ms. Atrial electrical activity is coarse. There are no ST-T wave changes suggestive of ischemia. QTc is 462 ms and QRS duration is normal.

## >> Was this a serious adverse event?

C1) Did the event result in death? **No**

C2) Was the event life-threatening (i.e., placed the subject at immediate risk of death from the event, as it occurred)? **No**

C3) Did the event result in inpatient hospitalization or prolongation of existing hospitalization? **Yes**

Dates of hospitalization: **From:** 10/07/10 **To:** 10/08/10

C4) Did the event result in a persistent or significant disability/incapacity? **No**

C5) Did the event result in a congenital anomaly/birth defect? **No**

C6) Based upon appropriate medical judgment, did the event jeopardize the subject's health and/or require medial or surgical intervention to prevent one of the other outcomes listed above, e.g., allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse?
**No**

## >> Protocol/Consent Forms

D1) Given this event's occurrence, are there revisions to the study or consent documents that you would like to submit at this time? **No**

## >> Corrective Action

E1) Have you established a corrective action plan to prevent future occurrence of the event? **Yes**

Describe the corrective action plan:

**While the safety protocols in place for this study worked as they planned, we will assess whether thre are additional screening tests that could be done to identify subjects who are likely to respond in a similar manner.**

## >> Attachments

There are no attachments for this event

**General Comments Regarding Adverse Event**
**Subject No. XCE-227**

**Comments by: Wayne Cascio, MD**

**Background and Events of 10/07/10:**

The subject is a 58 years old woman with previous history of volunteering for EPA sponsored health effects studies without incident. Relevant history is that she is overweight, hypertensive on medical therapy and has abnormal lipids. Based on prevailing definitions she has metabolic syndrome (increased BMI, hypertension and hypertriglyceridemia). The 12-electrocardiogram in atrial fibrillation shows a borderline increase in voltage but no other abnormalities.

The patient is reported to have had APBs prior to exposure. During the exposure an increase in the frequency of APBs was noted. As shown on the rhythm strips a brief run of what appears to be atrial fibrillation was recorded at 11:37:34. When a non-sustained run of SVT was recorded triggering an alarm it was decided to terminate the study and remove the subject from the chamber. Subsequent to that decision she developed a brief episode of atrial fibrillation and flutter that terminated spontaneously. At no time was the patient in distress.

The patient was transported to the UNC Hospitals Emergency Department where the subject remained overnight without incident. Subsequently, the subject has done well and returned to routine activities.

**Interpretation of Electrocardiograms:**

10/07/2010 Time 11:37:34 (Rhythm Strip)
Frequent APBs and one 7.5 second burst of supraventricular tachycardia. The rhythm is difficult to interpret as a full disclosure print-out but appears to be atrial fibrillation.

10/07/2010 Time: 11:44:40 (Rhythm Strip)
Atrial fibrillation and flutter converts to sinus bradycardia before reverting to atrial fibrillation.

10/07/2010 Time: 11:44:47 (Rhythm Strip)
Atrial flutter with 2:1 AV conduction. Mean heart rate 129 bpm. Atrial basic cycle length 240 ms corresponding to an atrial rate of 250 bpm. This rhythm appears to transition to atrial fibrillation that terminates leaving the heart in a sinus bradycardia.

10/07/2010 Time 01:49:xx
Probably slow atrial flutter with 2:1 AV conduction with mean rate of 120 bpm. Over the next few seconds the rhythm transitions to atrial fibrillation.

10/07/2010 Time: 01:56:01 (12-lead)
Atrial fibrillation with mean rate of 87 bpm. QRS 82 ms, QT 376 ms, QTc 452 ms. Non-specific T wave abnormalities in the inferior leads secondary to atrial fibrillation. Atrial electrical activity is coarse. There are no ST-T wave changes suggestive of ischemia. QTc is 462 ms and QRS duration is normal.

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10/07/2010 Time: 02:05:25 (12-lead)
Atrial fibrillation with mean rate of 91 bpm. QRS 82 ms, QT 388 ms, QTc 477 ms. Atrial electrical activity is coarse. There are no ST-T wave changes suggestive of ischemia. QTc is 462 ms and QRS duration is normal.

**Conclusion:** Adverse Event probably related to the study protocol.

**Comment:**
(1) While an increase of premature atrial beats has been reported in aged healthy people exposed to concentrated ambient fine PM, and in young healthy individuals and middle-aged healthy individuals exposed to traffic-related PM we are unaware of any study that demonstrates an increased risk of atrial flutter/fibrillation in healthy middle-aged individuals exposed to ambient or CAPS. An increase in the risk of atrial fibrillation has been described in a cohort of subjects with more advanced heart disease, i.e. individuals having internal cardiac defibrillators. For this reason the occurrence of transient atrial flutter and fibrillation was not anticipated.

(2) It is speculated that long-standing hypertension and systemic inflammation associated with metabolic syndrome increased the vulnerability of the atria to premature beats and that altered autonomic input related to exposure to particulate matter increased the frequency of premature atrial beats which initiated a short period of atrial flutter and fibrillation. It is important to appreciate that the electrophysiological substrate that permitted the atrial arrhythmia to persist was

present before the study was initiated and represents a chronic process. The susceptibility of the subject to the development of the atrial arrhythmia was not related to the exposure, yet it is likely that the exposure served to trigger the arrhythmia. The short duration of the arrhythmia also implies that the overall electrophysiological properties of the atria favor maintenance of a normal rhythm in contrast to a disorganized one.

(3) The staff identified the rhythm disturbance quickly and responded appropriately. It was prudent to have the patient transported to the emergency department. Subsequent evaluation did not identify any injury either transient or permanent.

(3) To limit the likelihood of such an episode from happening again it is recommended that the investigators consider obtaining an ambulatory ECG as part of the screening process and that subjects be excluded if they have >10 atrial or ventricular premature beats per hour. In an effort to be cost-effective and safe it would be reasonable to provide this additional screening to only subjects greater than 45 years of age, or those less than 45 years with a history of hypertension or diabetes.

Wayne Cascio

IRB Study #: 04-1677 (CTRC#2067)

Study Title: Physiological Changes in Adults with Metabolic Syndrome Exposed to Concentrated Ultrafine Chapel Hill Air Particles

PI: Robert Devlin, PhD

Sponsor: EPA

The Adverse event took place 10-7-2010 at the EPA Human Studies Facility on the UNC-CH campus

The volunteer (subject XCE-227) reported to EPA facility on 10-7-2010 to participate in the first of two exposure sessions for IRB#04-1677. The volunteer had previously undergone the same exposures for this protocol two years ago. The study progressed as expected and the volunteer entered the exposure chamber at 11:21am. All vitals were being monitored during the chamber exposure and were normal and consistent. The subject was reading and operating a remote control while in the chamber, which was contributing to several alarms being set off by the ECG for noise and the pulse oximeter for loss of tracing, this was noted by the investigator at the chamber, Candice Bailey, to be occurring due to physical movement of the subject's arms and fingers. At 11:44 automatic alarms sounded at the chamber consol and the medical station and an automatic ECG printout of an event was printed in the medical station. The subject's ECG reading indicated a 22 beat supraventricular tachycardia (SVT) lasting 10.5 seconds with 124bpm. After 10 seconds the subject's heart rate and rhythm were normal and all other vitals remained normal, the subject reported she was feeling fine. The study nurse, Maryann Bassett, consulted with the on-duty doctor, Terry Noah(UNC) and an EPA doctor, Dr. Andy Ghio and the decision was made to remove the subject from the chamber. Nurse Bassett proceeded to the exposure chamber to observe the subject and inform the investigator at the chamber, Candice Bailey that a decision was made to terminate the exposure as a precautionary measure. The subject was calmly informed the exposure would be ending. The exposure was stopped at 12:08 and the subject exited the chamber at 12:10pm and returned to the medical station to rest and be consulted with Nurse Bassett and Dr.Ghio.

Nurse Bassett removed the subject's ambulatory ECG (holter) monitor to review her heart rhythm prior to and during the exposure (meanwhile the subject's vitals were being monitored by telemetry), this holter monitor normally records for 24hrs. It was found that the subject had two arrhythmia events prior to entering the chamber, while in transit and not being monitored by the medical station's real-time telemetry. The first event occurred at 10:30am 3 beat SVT 133bpm, which occurred while the subject was walking and returning from the BAU at the CTRC. Another event was noted at 11:11am, 9 beat SVT for 3.68 sec 135bpm, while the subject was putting on the facemask and waiting to enter the exposure chamber. It was also noted that the subject had a high number of premature atrial contractions (PACs) throughout her visit.

After explanation and consultation with the subject, Dr. Ghio made an appointment for the subject to be seen at the UNC Cardiology Facility the next day, Friday 10-8-2010 at 1:40pm. The subject was informed that while these arrhythmias were not an indication of eminent danger, it did indicate

CBS 10/12/10

there may be an underlying issue that should be examined by a cardiologist soon. Prior to the subjects departure and while sitting quietly, the subject's heat rhythm changed and went into an unorganized atrial fibrillation that set into a brief period at atrial flutter. Since the subject's condition appeared to be worsening or changing, the medical station nurses and physicians decided that the subject should be transferred to the ER to be monitored in a hospital setting. It was determined that the safest route would be for her to be transported by EMT. The subject still reported feeling physically fine and agreed to the assessment by Dr. Ghio and Dr. Carraway that she should be transported to the ER. The NHEERL Human Studies Research Director, Dr. Howard Kehrl was briefed on the situation. Nurse Bassett called 911 and informed the Orange County EMS of the situation. The Security officer was also notified that the Orange County EMTs would be coming shortly. The EMTs arrived within about 5 min. They hooked the subject up to their own ECG equipment. The subject was sent off with her belongs and copies of pertinent ECG readings recorded while at the EPA and told that we would phone her in the morning to check on her status. The subject went to the restroom and got on the stretcher, her sinus rhythm was normal at this point. She departed via ambulance at 3:05pm.

Nurse Bassett spoke with the subject the following day, Friday 10-8-2010, and she said she had been admitted and observed overnight and the cardiologist said everything looked relatively normal. She was to undergo an echocardiogram (and possibly a stress test) later that day and would then let the doctor determine if she should go for the cardiologist appointment that had been made (by Dr.Ghio at the EPA) for that afternoon. The results from the echocardiogram showed no major cardiovascular issues. The subject was very thankful for the safety measures that were taken at the EPA.

It is our summation that this subject had an underlying arrhythmia, atrial irritability or other pathology that was not observed during her recent physical (date) (with ___ min of ECG readings), and she should have been excluded from participating in the study. Additionally of note, in her previous XCON exposures 2 years ago (with 24hrs of ECG monitoring) these arrhythmia arrhythmias were not present. Arrhythmias during PM exposures are not an Unanticipated Problem, however the length or severity in this cases classifies as an Adverse Event, since it was an "unfavorable medical occurrence" and is being filed with the UNC IRB. We can only conclude that the atrial fibrillation and atrial flutter were possibly related to the research , however they could also be related to the presence an underlying arrhythmias. There were no deviations from the IRB protocol and all safety measures were taken and in place. An Adverse Event report is being filed with the UNC IRB at this time.

There is always room for improvement, and the following recommendations for improvement and safety:

-To further evaluate any possible arrhythmias or underlying heart conditions of enrolled XCON subjects, they will be evaluated after 24hr holter monitoring before their exposure date.
-Automatic ECG printouts at the exposure chamber, if the heart rate is over 120bpm or other arrhythmias are detected
-CPR training for individuals sitting at the chamber consol
-Basic training for ECG and heart rhythm monitoring for individuals sitting at the chamber consol

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

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**To**: Robert Devlin
Pediatrics
CB: 7315

**From**: Biomedical IRB

_____
Authorized signature on behalf of IRB

**Date**: 10/20/2010

**RE**: IRB review of Unanticipated Problem report
**Submission Type**: Unanticipated Problem
**Study #:** 04-1677 (Former IRB Number GCRC-2067)
**Other #:** CTRC : 2067
**Study Title**: Physiological Changes in Adults with Metabolic Syndrome Exposed to Concentrated Ultrafine Chapel Hill Air Particles

**Submission Description:**

Subject experienced tachycardia and atrial fibrillation while engaged in a study in the Human Studies Facility. Subject pursuing medical follow up. No other adverse sequelae reported at this time.

Based on the IRB's review of your report of an unanticipated problem, it has been determined that no additional information is required and no changes in the study are warranted.

CC:
Mike Schmitt, Environmentally Protection Agency
Candice Bailey, Epa
Robert Truckner, (EPA), Non-IRB Review Contact
Wanda Simmons, (CTRC), Non-IRB Review Contact