

Forskningsprogram SNAP X REPROSAFE FLIPP			
Projekttitel (svensk): ALVA - Luftföroreningar och livshotande kammararytmier			
Projekttitel (engelsk): ALVA - Air Pollution and Life Threatening Ventricular Arrhythmia			
Huvudsökande	Efternamn: Bellander	Förnamn: Tom	Födelseår: 1950
	Organisation: Stockholms läns landsting		Institution: Arbets- och miljömedicin
	Adress: Norrbacka III	Postnr: 171 76	Ort: Stockholm
	Telefon: 08-5177 7906	E-post: Tom.bellander@imm.ki.se	Tjänst: Bitr enhetsch (docent)
Medsökare	Efternamn, förnamn, tjänst, organisation, institution:		
	Telefon	E-post	Kvinna <input type="checkbox"/> Man <input type="checkbox"/>
<p>Sammanfattning på svenska strukturerad enligt följande: 1) Projektets betydelse för programmet 2) Miljörelevans och förväntad betydelse för miljöpolitiken 3) Mål och hypotes 4) Metodik och genomförande 5) Kommunikationsinsatser i relation till programmet:</p> <p>Ett flertal studier har det senaste årtiondet bekräftat att dag-till-dagvariationer i luftföroreningsnivåer är förknippade med variationer i dödstal och sjukhusinläggningar. Effekten per enhet luftförorening förefaller vara lika stor eller större vid lägre medelnivå som vid högre medelnivåer. Om dessa resultat kan bekräftas innebär det att ytterligare hälsovinster kan göras vid förbättringar av den redan internationellt sett relativt goda luftföroreningssituationen i svenska tätorter. Det är dock fortfarande osäkert vilka de aktuella mekanismerna skulle vara och därmed också vilken del av befolkningen som mest skulle dra nytta av en förbättring av luftmiljön. En studie av patienter i Boston med inopererade defibrillatorer (ICD) har visat att luftföroreningar kan öka risken för kammararytmier, vilket kan vara en del i förklaringen av det biologiska sambandet. Studien är dock liten och med knapphändig information om patienterna vilket gör resultaten något svårtolkade.</p> <p>Målet med den här föreslagna studien är att analysera sambandet mellan dagliga variationer i luftföroreningsnivå och risken för kammararytmi, i patienter med så hög grundrisk att drabbas av arytmier att de fått en inopererad defibrillator. Hypotesen är att risken är förhöjd i nära anslutning till att luftföroreningsnivåerna varit höga.</p> <p>Försökspersonerna rekryteras via hjärtmottagningar i Stockholm, Göteborg och Malmö. Rekryteringen startade vid hjärtmottagningen vid Karolinska sjukhuset i mitten av 2002 och har sedan successivt utvidgats. Till september 2003 har sammanlagt 63 patienter rekryterats och 33 tillslag noterats. Detta är lägre än förväntat och rekryteringsperioden kommer därför att förlängas jämfört med den ursprungliga planen. Alla patienter svarar på frågor om bakgrund och livsstilsfaktorer, och vid tillslag kontaktar dessa en sköterska vid mottagningen som samlar in uppgifter om omständigheterna vid tillslaget. Den exakta tidpunkten och andra uppgifter om tillslaget lagras i defibrillatort och tas tillvara vid nästa besök på mottagningen. Sambandsanalysen kommer att utföras med "case-crossover" metodik, som gör det möjligt att - med full kontroll för individuella faktorer som varierar med tiden - jämföra luftföroreningsnivåerna strax före tillslaget ("fallperiod") med dem vid en eller flera kontrollperioder, när patienten inte hade en arytmier. Uppgifter om dagliga nivåer av olika luftföroreningar insamlas i efterhand från lokala miljö- och hälsoskyddskontor. Resultaten från studien kommer att redovisas vid nationella och internationella konferenser samt rapporteras till den vetenskapliga litteraturen.</p>			
Summa sökta medel per år i kr:		År 2004	År 2005
		361 480	387 348

Sökta projektmedel fördelade på kostnadslag	År 2004 (k)	År 2005 (k)
Personalkostnad inkl. soc. avgifter*		
Petter Ljungman, leg läk, 25% (2*12*0.25*1.54*30 000 = 277 200)	138 600	138 600
Ej rekryterad, Senior statistiker, 10% (2*12*0.1*1.54*30 000 = 110 880)	55 440	55 440
Tom Bellander, docent, 10% (2*12*0.1*1.54*40 000 = 147 840)	73 920	73 920
Övriga omkostn exkl moms (förbrukningsmtrl, analyser, resor etc)**	10 000	30 000
Resor (1 resa utomlands a 15 000, 5 resor inom Sverige a 5 000)		
Delsumma av ovanstående poster:	277 960	297 960
Förvaltningspåslag:30.... %	83 388	89 388
Totalsumma per år: (införs sid. 1):	361 480	387 348

*) Specificera namn, tjänst **) Specificera

Samtliga övriga miljörelaterade projekt för vilka de sökande har beviljats anslag eller söker anslag för 2004-2006. OBS Även EU-finansiering.

Projekttitel	Finansiär	Tidsperiod	Sökt kr	Beviljat kr
INTERVENT	SNAP/NV	2004-5	3 062 880	
SENSI	SNAP/NV	2004-5	830 000	830 000
AIRGENE	EU	2004-5	1 444 176	1 444 176
Luftkvalité i små barns inomhusmiljö	SNAP/NV	2004-5	1 033 000	1 033 000

**Miljörelaterade projekt för vilka sökande har beviljats anslag för 2000-2003
OBS Även EU-finansiering**

Projekttitel	Finansiär	Tidsperiod	Beviljat Kr
ALVA	NV/Formas	2001-3	1 320 000
SENSI	NV/SNAP	2003	499 969
AIRGENE	EU	2003	979 560
Luftkvalité i små barns inomhusmiljö	NV/SNAP	2002-3	859 916
Cohort feasibility	NV/SNAP	2002-3	297 000
INDEX	VV	2000	333 333
ONSET	NV/SNAP	2002-2003	500 000

Datum och sökandes underskrift, vilken samtidigt ger Naturvårdsverket tillåtelse att publicera sökandes namn på sin webbplats:	Datum och underskrift av prefekt eller motsvarande med namnförtydligande:
Tom Bellander	Göran Pershagen

Ansökan skall bestå av detta formulär jämte högst sex sidor lång projektbeskrivning på **engelska** (strukturerad som den svenska sammanfattningen samt en redovisning av kunskapsläget). Referenser till egna publikationer ges med sifferhänvisning till CV. Andra referenser ges i löpande text. Sökandes och eventuell medsökandes CV får omfatta högst två sidor. Inga bilagor kommer att beaktas vid bedömning. Ansökan (max 10 A4-sidor, 12 punkters teckenstorlek) skall inlämnas i **original + 15 kopior samt elektroniskt** till ansok@naturvardsverket.se. Häfta ihop ansökan och använd hålat papper. Ansökan skall ha inkommit senast den 15 oktober 2003 till Naturvårdsverket, Forskningssekretariatet, 106 48 STOCKHOLM.

ALVA - Air Pollution and Life Threatening Ventricular Arrhythmia

Tom Bellander, Dept. of Environmental Health, Stockholm County Council
Göran Pershagen, Institute of Environmental Medicine, Karolinska Institutet
Petter Ljungman, Cardiology Clinic, Södersjukhuset
Niklas Berglind, Dept. of Environmental Health, Stockholm County Council
Fredrik Gadler, Cardiology Clinic, Karolinska Hospital
Bengt Sjögren, Institute of Environmental Medicine, Karolinska Institutet

This project is fully financed up until the end of 2003 from the Swedish National Environment Protection Agency. Additional financing is sought for the remaining study period.

Present state of knowledge

Several studies have shown associations between day-to-day variations in ambient air pollution levels and acute cardiovascular hospitalization (Schwartz 1999) as well as total mortality and specific mortality in cardiovascular disease (Schwartz 1994). The basic design in these studies have been to correlate time series of measured air pollutants that to register data on the number of persons that each day are admitted to hospitals or died from cardiovascular disease. The analyses of the time series have generally been adjusted for meteorological factors and allowed for some lag between exposure and health event. Several different pollutant has been linked to the health events in the different studies, e.g. PM₁₀ (particulate matter less than 10 µm in diameter), CO (carbon monoxide) and NO₂ (nitrogen dioxide). There are recent results that suggest that increased levels in the low to moderate range show a stronger association with negative health effects than the same increase in the high level range (Schwartz 2000).

It is still unclear which biological mechanisms may be behind the observed effects. A number of studies, both experimental and epidemiological, have been conducted in order to investigate these mechanisms and a summary of the current state of the science was recently published (Pope 2000). Several studies have supported the theory that air pollution, and especially exposure to particles, through alveolar inflammation in the lungs, lead to changes in the blood's coagulation properties and affects the autonomous nervous system. Changes in blood viscosity, heart rate and heart rate variability are activated by the autonomous nervous system and may increase the risk for serious acute cardiovascular events, such as infarctions and arrhythmia. One study from Boston, USA (Peters et al, 2000) have shown that increased daily ambient levels of NO₂, CO and particles are related to the incidence of ventricular arrhythmia in subjects with Implanted Cardioverter Defibrillators (ICD). The study subjects were followed for on average one year and nine months. Out of the 100 subjects 33 had any intervention from the ICD-device and only six had 10 interventions or more. No individual information about the subjects was available and they were spread out over a large geographical area. This lack of individual information along with the fact that the strongest relation were found in the group of six individuals with many interventions makes the results somewhat difficult to interpret. Other similar studies in the US and the UK are ongoing, but none have so far been reported in peer-reviewed publications.

Thus there is quite strong evidence that ambient air pollution has a negative effect on cardiovascular disease and that increased levels may act as a trigger for arrhythmia. Whether or not temporarily increased levels of air pollution have an impact on the incidence of cardiac arrhythmia in the moderately polluted cities of Sweden is still unknown.

Environmental relevance and expected significance for environmental policy

There is a great lack of effect studies in the low to moderate air pollution levels, and the results of any study of health effects in the air pollution range we have in the Swedish cities is of great scientific and practical importance. Recent studies suggests that some of the acute effects connected to an increase in the air pollution level are at least as strong at a low base level as at higher levels. If this evidence are supported and strengthened, great gains in the public health can be achieved by improving the air quality even in the relatively clean Swedish cities. Increased mortality and morbidity in periods of high air pollution levels has been seen in many studies over the last decade, and the scientific community is in agreement that the relationship exists. It is, however, still unclear which segments of the population that **are** affected. The results of this study will contribute to identify groups within the general population that are potentially sensitive to the negative effects of air pollution and help clarify how the mechanisms behind this association work.

Aims and hypothesis

The aim of this study is to analyze the relation between short time variations in ambient air pollution levels and ventricular arrhythmia. By utilizing the information on time and type of arrhythmia stored in the ICD-device this relation can be investigated. Information on other potential triggers like physical exercise, alcohol consumption and respiratory infections will also be collected and give us the opportunity to study how air pollution interact with other factors. The hypothesis is that high levels of air pollution can trigger ventricular arrhythmia, either in itself or by interaction with other factors.

Methods

The relation between day-to-day variations in air pollution levels and ventricular arrhythmia will be analyzed with the case-crossover method. This study design was developed to study triggers for myocardial infarction (Maclure 1991) and has in recent years been used to study a number of different triggers for disease (Maclure & Mittleman 2000). The method has also been used to study the effect of air pollution (Neas et al 1999) and was the method used in the study of air pollution and arrhythmia in ICD-patients in Boston (Peters et al 2000). In the case-crossover method only cases are studied and their exposure prior to the health event is compared to their exposure in one or more control periods that did not precede a health event. In the proposed study, a specified time interval prior to each point in time when an ICD-device makes an intervention will be defined as case-period, i.e. the period in time when exposure that triggered the arrhythmia may have occurred. The average air pollution levels in the case-period is compared to the average levels in two control-periods of the same length as the case-period, chosen symmetrically one week before and after the ICD-intervention. Exposure preceding each arrhythmia is compared to exposure not preceding an arrhythmia in the same person. The cases are their own controls and individual factors that are stable over time will be controlled for by design. Factors that may have confounding effects on the association between air pollution exposure and ventricular arrhythmia are only those that vary over time These can be internal factors, e.g. physical exercise, alcohol consumption and respiratory infections as well as external, such as meteorological and geographical factors. By comparing exposure to other potential triggers in the case period to the stated normal frequency of these exposures, collected at recruitment to the study, the case-crossover method allows us to study whether or not these factors can interact with air pollution as trigger for

arrhythmia. Groups of individuals who are especially sensitive to the effects of air pollution can be identified.

Implementation

All ICD-patients living in Stockholm, Västra Götaland and Skåne counties will be asked to participate. They are offered to participate in the study regardless of their current disease status and regardless of whether they have experienced a discharge from their ICD-device or not. Only patients whose permanent residence lies within areas for which the variation in air pollution levels at the central monitors can be considered relevant are included in the final study.

Following the starting date all current patients who visit their clinic for their regular six-month check-up and all new patients will be asked to participate. Recruitment was originally planned to go on for six months and each patient to be followed for 2 years. Difficulties in establishing the study in the clinical settings have delayed the start of recruitment (see time plan below). The number of patients available seems also lower than anticipated. At recruitment, the patients who accept to participate answer a written questionnaire containing questions on basic lifestyle factors and factors that can influence their exposure to air pollution. From the hospital journal information about the patient's existing cardiovascular disease, diabetes, medication, height and weight is collected. The information about time and frequency of certain activities will be used to estimate the normal frequency of potential triggers and will be used when analyzing whether or not a certain activity is more frequent immediately before an arrhythmia than at other times. Background information will be used to divide the subjects in subgroups to see if those who are sensitive to the effects from air pollution can be identified.

The subjects are asked to call a contact person at their clinic immediately after each intervention from their ICD. The contact person asks the participants standardized questions regarding the intervention comprising detailed descriptions of the two hours immediately preceding the intervention and descriptions of activities during the seven days before the intervention. The most important activities are those which can be potential triggers, i.e. changes in their existing cardiovascular disease, changes in their medication, physical exercise, and factors that can influence their exposure to air pollution such as time spent outdoors, exposure to local sources (smoky rooms, lawnmowers etc.). This information is used to estimate individual exposure to air pollution and, together with information about normal frequency of potential triggers, to investigate their effects.

At the time of each patient's regular six-month check-up the log from the ICD-device is downloaded and saved to a computer disc. The treating physician makes an assessment of each intervention and the subject is asked for each arrhythmia if the call to the contact person has been made. Otherwise the subject will answer the same standardized questions as in the telephone interview, however it is less likely that a detailed description of the hours and days preceding the intervention could be obtained..

Hourly averages of air pollution levels are routinely collected at central monitors in the study area. Nitrogen dioxide, ozone and sulfur dioxide is measured in all study areas. In Malmö city there are also measurement of PM10. In Gothenburg there are measurements of PM10 and carbon monoxide and in Stockholm PM10, PM2.5 and carbon monoxide is measured. During parts of the study period the projects PASTA and HEAPSS will measure ultrafine particle counts in Stockholm and the results from the HEAPSS project may be used to estimate ultrafine particle exposure for all subjects. SMHI collect hourly averages for temperature,

barometric pressure, precipitation, wind, and relative humidity in all areas. Air pollution and weather data will be acquired through the local environment and health protection administrations and SMHI respectively.

In the Boston study of air pollution and arrhythmia 33 out of 100 subjects experienced at least one ICD-intervention during an average follow-up time of one year and nine months. A total of 223 interventions in an average follow-up time of one year and eleven months was registered for the 33 subjects with at least one intervention, which corresponds to 3.5 interventions per person and year. In Stockholm County there are currently about 300 ICD-patients and there are approximately 200 each in Västra Götaland and Skåne counties, leading to a total study base of 700 individuals. Assuming a participation rate of 80% after exclusion of those without reliable exposure information and those who choose not to participate, we will arrive at a total of 560 subjects in the study. With 24 months of follow-up for each person, 38% or circa 210 persons will have at least one ICD-intervention. With on average 7 interventions per subject we will be able to compare 1480 case periods with the double amount of control periods. With a statistical power of 80% and a significance level of 5% we will be able to find a difference in average nitrogen dioxide levels between case and control periods of 0.9 µg/m³. The differences for particles and carbon monoxide that can be detected will be about the same.

Approval from the ethical committees has been obtained for the participating departments of cardiology at Karolinska Hospital, Huddinge Hospital, Södersjukhuset (all in Stockholm) and Sahlgrenska hospital (Göteborg). Approval will be sought in Malmö during fall 2003. The data collection is not considered to be inconvenient for the participating subjects. Data collection started in the second half of 2002 in Karolinska and Huddinge, and in August 2003 in Södersjukhuset and Sahlgrenska. So far 63 patients have been enrolled, of which 33 have had interventions. Data collection in Malmö can start in the end of 2003.

Dissemination of results

The results from the study will be presented at national and international scientific conferences, both in environmental health and cardiology, and will be published in international scientific journals in the field of environmental medicine. The results will also be presented in Swedish reports aimed at public agencies and the general public.

Time plan

Data collection started in July 2001 and was planned to go on for 30 months. The data management phase was planned to be from January through March 2004 and air pollution and weather data for the period will be acquired. The analysis was planned to start in April 2004 and the results to be published in December 2004. Due to the difficulties in establishing recruitment in the different clinical settings and the lower number of recruited subjects than anticipated, it is necessary to prolong recruitment throughout most of the data collection period that is suggested to be extended to the end of 2004, with reporting in the end of 2005.

Budget

Funding is requested for 2004 and 2005. The study years 2001-2003 are already covered by separate funding. The requested funding will cover salary for research physician (PhD student; 25%; 277 000), senior statistician (10%; 111 000), principal investigator (10 %; 148

000), travel (40 000), and university overhead (30%; 173 000). The requested funding has been adjusted according to the fact that the finishing of the project is postponed and thus part of the received funding for 2003 may be used in 2004-5.

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CV of Tom Bellander

Tom Bellander was born in 1950, obtained MSc in 1976 and PhD in 1987. His previous line of research was occupational hygiene and epidemiology (1974-1997). His current interest is in environmental epidemiology and in particular the exposure characterisation in population studies. TB holds a position as assistant director of the Unit of Environmental Health within the Department of Occupational and Environmental Medicine, Stockholm County Council, and is also associate professor at the Institute of Environmental Medicine, Karolinska Institutet, Stockholm. One of his doctorate students has obtained the doctoral degree and TB is currently the main tutor of two doctorate students. TB has repeatedly served as temporary expert at the WHO. TB has been involved in a leading role in many national and international research projects, and has co-authored more than 40 original papers.