

REVIEW

Why cardiologists should be interested in air pollution

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Despite major improvements in air quality resulting from increasingly stringent legislation, there remains a strong association between daily mortality and current levels of air pollution. Growing epidemiological evidence suggests that many, perhaps the majority, of these deaths are caused by cardiovascular disease.

Urban air pollution is primarily derived from fossil fuel combustion and consists of both gaseous and particulate matter (PM) (table 1). Airborne particles are complex mixtures of elemental carbon, organic carbon compounds, and reactive components such as transition metals, metal oxides, acid condensates, sulfates, and nitrates. The particles believed to be most deleterious to health are those with an aerodynamic diameter of less than 10 μm (PM_{10}) although increasingly attention has focused on the ultrafine component ($\text{PM}_{2.5}$ and $\text{PM}_{0.1}$), which can penetrate deep into the gas exchange region of the lung. Sulfur dioxide is largely derived from industrial sources while nitrogen dioxide and carbon monoxide are both vehicle derived. Ozone is an oxidant gas formed by the action of ultraviolet light on oxides of nitrogen and hydrocarbon fragments in vehicle emissions. All have been implicated in time series analyses as causes of adverse cardiovascular health effects (tables 1 and 2).¹⁻¹⁶

ACUTE CARDIOVASCULAR EFFECTS

Examination of epidemiological data shows that while the relative risk for pollution related death is greater for respiratory than for cardiovascular causes, because of the size of the population at risk, the number of deaths is in fact greater for cardiovascular diseases¹⁷ (table 2). Although effect sizes vary greatly between studies, meta-analyses of the time series data suggest that an increase in fine particulate pollution of 10 $\mu\text{g}/\text{m}^3$ is associated with an increase in total mortality of 1.8% and cardiovascular mortality of about 1.4%.^{6,7} Similar conclusions can be drawn from data on hospital admissions for cardiovascular disease (table 3).¹⁸⁻²⁶ Findings from a London time series analysis were consistent with 1 in 50 myocardial infarctions treated at London hospitals being triggered by outdoor air pollution. By extrapolation, across the UK high levels of ambient pollution may be responsible for at least 6000 cardiovascular events per year.²⁵ A systematic review of the time series data, prepared for the Committee on the Medical Effects of Air Pollutants, UK Department of Health, estimated that a 10 $\mu\text{g}/\text{m}^3$ reduction in 24 hour average

PM_{10} concentration would be associated with a 0.8% reduction in cardiovascular admissions.²⁷ A recent observation from Dublin suggests that these data may even underestimate the true benefit of achievable reductions in particulate pollution. A ban on coal sales in 1990 that reduced black smoke concentration by 35.6 $\mu\text{g}/\text{m}^3$ was associated with a 10.3% decrease in annual cardiovascular mortality.²⁸ In a similar intervention study, a 50% reduction in sulfur dioxide concentrations following legal restrictions on fuel oil sulfur in Hong Kong was immediately followed by a 2.4% reduction in cardiovascular deaths.²⁹

Survival analysis data derived from cohort studies have also defined the population that is most susceptible to the cardiovascular effects of air pollution. The highest risk appears to be in people with pre-existing cardiac disease. Goldberg and colleagues,³⁰ for example, showed that daily mortality increased linearly with the concentration of ambient particles among people who had chronic coronary artery disease and congestive heart failure. While the relations between cardiovascular mortality and air pollution have been repeatedly shown, the precise causes of these deaths have been more difficult to determine. The majority of time series studies describe effects according to broad categories, relying on retrospective analysis of routine coding for both admissions and mortality. During a smog episode in West Germany in 1985, however, deaths and admissions were coded on the basis of the *International classification of diseases* for 94% of cases.¹ Deaths from heart failure, myocardial infarction, and stroke were all increased significantly in the polluted compared with the control areas. Notably, arrhythmia admissions were increased by 50% compared with the periods before and after the smog.¹ More recently Hoek and colleagues³¹ studied associations between daily variations in air pollution and specific cardiovascular causes of death in the Netherlands over eight years. Effect sizes were significant for total cardiovascular mortality and deaths caused by myocardial infarction and other ischaemic heart disease, but were most pronounced (three times higher) for deaths caused by heart failure and arrhythmia.³¹

A panel study carried out by Peters and colleagues³² adds further weight to the hypothesis that an increase in cardiac arrhythmia contributes to the rise in mortality associated with increases in ambient pollution levels. In 100 patients with implantable cardioverter-defibrillators in Boston in the USA, episodes of defibrillation were related to daily air pollution. The frequency of defibrillator discharges was

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Table 1 Sources of urban air pollution

	London annual hourly average 1996	Maximum daily UK value 1996	EPAQS
Sulfur dioxide (ppb)	8	201	100 (over 15 minutes)
PM ₁₀ (µg/m ³)	30	380	50 (24 hour mean)
Ozone (PB)	16	121 (rural site)	50 (8 hour running average)
Nitrogen dioxide (PB)	28	205	150 (1 hour mean)
Carbon monoxide (ppm)	1.4 (roadside)	15.8 (roadside)	10 (8 hour running average)

EPAQS, Expert Panel on Air Quality Standards (Department for Environment, Food and Rural Affairs); PM₁₀, particulate matter with an aerodynamic diameter of less than 10 µm.

Table 2 Time series analyses of pollutants causing adverse cardiovascular health effects

Time series study	Geographic area	Pollutants	CVS mortality effect
Wichmann 1985 ¹	West Germany 1985	SO ₂ TSP	8% ↑ mortality during smog 6% ↑ CVS mortality (15% ↑ admissions)
Schwartz 1990 ²	London 1958–1972	Black smoke, SO ₂	Significant predictors of all cause mortality
Katsouyanni 1990 ³	Athens 1975–1982	SO ₂ , black smoke	Higher respiratory and CVS mortality on polluted days
Kinney 1991 ⁴	Los Angeles County 1970–1979	Particles, CO, NO ₂	Strongly associated with daily CVS mortality
Schwartz 1992 ⁵	Philadelphia 1973–1980	SO ₂ TSP	5% ↑ mortality/100 µg ↑ 7% ↑ mortality/100 µg ↑, 10% ↑ CVS mortality
Dockery 1993 ⁶	6 US cities	Fine particles, sulfates	Association between cardiopulmonary mortality and level of pollution in city
Schwartz 1994 ⁷	Philadelphia death certificates 1973–1980	TSP	RR death = 1.08 on high v low pollution day, ↑ heart disease and stroke deaths
Schwartz 1994 ⁸	Meta-analysis	TSP	RR death = 1.06 for 100 µg ↑
Anderson 1996 ⁹	London 1987–1992	Black smoke SO ₂	2.5% ↑ daily mortality/7–19 µg/m ³ ↑ SO ₂ also significant
Ponka 1998 ¹⁰	Helsinki 1987–1993	Ozone PM ₁₀	3.6% ↑ CVS mortality/7–36 PB ↑ 4.1% ↑ CVS mortality/10 µg/m ³ ↑
Zmirou 1998 ¹¹	10 European cities	Ozone NO ₂	9.9% ↑ CVS mortality/20 µg/m ³ ↑ Additive effect with PM ₁₀ and ozone
Zmirou 1998 ¹¹	10 European cities	Black smoke	RR CVS mortality 1.02/50 µg/m ³ ↑
Ostro 1999 ¹²	Bangkok 1992–1995	SO ₂	RR CVS mortality 1.04/50 µg/m ³ ↑
Rossi 1999 ¹³	Milan 1980–1989	PM ₁₀ TSP	2% ↑ CVS mortality/10 µg/m ³ ↑ 7% ↑ heart failure deaths/100 µg/m ³ ↑, 10% ↑ myocardial infarction mortality/100 µg/m ³ ↑
Samet 2000 ¹⁴	20 U cities 1987–1994	PM ₁₀	↑ Rate of CVS/respiratory mortality, 0.68% for each ↑ PM ₁₀ of 10 µg/m ³
Kwon 2001 ¹⁵	Seoul 1994–1998	SO ₂ , CO, ozone, NO ₂ PM ₁₀ , SO ₂ , CO, ozone NO ₂	Weak associations RR mortality 1.014/IQR ↑ PM ₁₀ RR mortality 1.020/IQR ↑ CO Effect 2.5–4.1% higher in CCF
Katsouyanni 2001 ¹⁶	29 European cities APHEA 2	PM ₁₀	↑ Rate of CVS/respiratory mortality 0.6% for each ↑ PM ₁₀ of 10 µg/m ³ , effect size greater in elderly, with high NO ₂ , or in cold climates

APHEA, Air Pollution and Health: a European approach; CCF, congestive cardiac failure; CVS, cardiovascular system; IQR, interquartile range; RR, relative risk; TSP, total suspended particles.

Table 3 Hospital admissions for cardiovascular disease

Time series study	Geographic area	Pollutants	Effect on CVS admissions
Schwartz 1995 ¹⁸	Michigan 1986–1989	PM ₁₀ , CO	↑ Ischaemic heart disease admissions (RR 1.018 IQR ↑ PM ₁₀) and with heart failure (RR 1.024 /IQR ↑ PM ₁₀ and 1.022/ IQR ↑ CO)
Burnett 1995 ¹⁹	Ontario 1983–1988	Particulate sulfates	2.8% ↑ CVS admission/13 µg/m ³ ↑
Morris 1995 ²⁰	7 US cities 1986–1989	CO	↑ Heart failure admissions (RR 1.10–1.37/10 ppm ↑)
Wordley 1997 ²¹	Birmingham 1992–1994	PM ₁₀	↑ Risk of respiratory (2.4%) or cerebrovascular (2.1%) admission for 10 µg/m ³ ↑
Schwartz 1997 ²²	Tuscon 1997	PM ₁₀ CO	2.75% ↑ CVS admission/IQR ↑ 2.79% ↑ CVS admission/IQR ↑
Burnett 1997 ²³	10 Canadian cities 1981–1991	Ozone/SO ₂	Little association
Burnett 1997 ²⁴	Toronto 1992–1994	CO	RR heart failure admission 1.065/IQR ↑
Poloniecki 1997 ²⁵	London 1987–1994	Ozone, NO ₂ , SO ₂ Black smoke	13% ↑ CVS admissions/IQR ↑ gaseous pollutants 2.5% myocardial infarction admissions attributable, associated with angina admissions
Schwartz 1999 ²⁶	Eight US counties 1988–1990	NO ₂ PM ₁₀ CO	Associated with arrhythmia admissions 2.48% ↑ CVS admission/IQR ↑ 2.79% ↑ CVS admission/IQR ↑

significantly correlated with increased PM₁₀ and PM_{2.5}, with a lag time of two days, and with nitrogen dioxide on the previous day. In patients with at least 10 interventions to treat ventricular arrhythmia, the odds of a discharge tripled with an increase in nitrogen dioxide from the 5th to 95th centile and increased by 60% for an equivalent rise in PM_{2.5}.

The relation between air pollution and myocardial infarction has recently been strengthened by the findings of the determinants of myocardial infarction onset study.³³ This multicentre, case crossover investigation suggested that a transient increase in the concentration of fine particles (increase of 25 µg/m³ PM_{2.5})—still below current air quality standards—was associated with an increased risk (odds ratio 1.48) of myocardial infarction within 1–2 hours. In addition high 24 hour concentrations of fine particles were associated with an increased risk (odds ratio 1.69) of myocardial infarction. The results at the two separate time periods were independent and additive suggesting the possibility of two, possibly independent, mechanisms.

POTENTIAL MECHANISMS

Epidemiology has clearly shown a link between increases in particulate air pollution and deaths and admissions caused by heart failure, myocardial infarction, and arrhythmia. To show that these associations are causal, plausible mechanisms of action are required. Several hypotheses have been proposed, and evidence is accumulating in support of two possibly interlinked mechanisms by which low concentrations of particles in inspired air may have adverse cardiovascular effects. Inhalation and interstitialisation of fine particles may provoke an inflammatory response in the lungs with the consequent release into the circulation of prothrombotic and inflammatory cytokines. A systemic acute phase response of this nature would put people with coronary atheroma at increased risk of plaque rupture and thrombosis. Secondly, exposure to PM may have an adverse effect on cardiac autonomic control, leading to an increased risk of arrhythmia in susceptible patients.

INFLAMMATION AND COAGULATION

A systemic inflammatory response to particulate air pollution was initially suggested in 1995 by Seaton and colleagues³⁴ who postulated that such a response may precipitate acute coronary events as a result of an increase in blood coagulability. The relation between systemic inflammation and adverse coronary events both in patients with coronary artery disease^{35–36} and in the general population³⁷ is now well established. The analysis of stored blood samples from the subjects of large epidemiological studies has provided evidence for a systemic inflammatory response to air pollutants. Both plasma viscosity and C reactive protein concentration increased in association with high levels of particulate pollution in studies involving nearly 4000 healthy adults.^{38–39} During an air pollution episode, the odds of observing C reactive protein concentrations above the 90th centile increased threefold, and the odds ratio for plasma viscosity above the 95th centile of the distribution was 3.6. These associations suggest that pulmonary injury as a result of pollution may lead to a systemic inflammatory response. The pulmonary insult initiating such a sequence of events has been shown by exposure studies at both the cellular and animal level. Fine particles have been shown to be able to penetrate the alveolar epithelium,⁴⁰ causing local inflammation and oxidative stress.⁴¹ Human bronchial epithelial cells exposed to combustion derived particles *in vitro* release proinflammatory cytokines such as interleukin 6, interleukin 8, and tumour necrosis factor α .^{42–43} Cytokine production in these models is preceded by activation of the transcription

factor nuclear factor κ B^{44–45} and is inhibited by the free radical scavenger *N*-acetyl-L-cysteine.⁴⁶

In animals, ambient PM₁₀ samples collected and then administered by intratracheal instillation have enabled closer investigation of the properties of particles that are responsible for causing an inflammatory response.⁴⁷ The degree of oxidative stress and the release of cytokines have consistently been found to be related to size, surface area, and the transition metal content of particles.^{48–49} The oxidant and proinflammatory properties of particles remain an active area of research, while the systemic and cardiac consequences of this pulmonary injury are now also being examined experimentally. In healthy human volunteers, increases in neutrophils and platelets in the peripheral blood have been found following acute exposure to diesel exhaust, in association with an increase in inflammatory cells and expression of endothelial adhesion molecules in bronchial biopsies.⁵⁰ In hyperlipidaemic rabbits, exposure to PM₁₀ caused bone marrow stimulation, with an increase in circulating polymorphonuclear leucocytes. In addition, atherosclerotic lesions in these animals displayed characteristic features of instability (thin plaque caps, presence of inflammatory cells, fewer smooth muscle cells) when compared with lesions in non-exposed controls.⁵¹

Recently, the assumption that local pulmonary inflammation following pollution exposure is the sole trigger of the systemic inflammatory response has been challenged. Ultrafine carbon particles radiolabelled with 99 m technetium were found to pass rapidly into the systemic circulation following inhalation.⁵² Accumulation in the liver, perhaps by Kupffer cells, suggests that inflammation in response to pollution may be initiated at extrapulmonary sites. Animal and human challenge studies should further clarify the nature of the proinflammatory and procoagulant cytokine responses to inhalation of specific pollutants.

CARDIAC AUTONOMIC CONTROL

Disturbances in the control of heart rate and rhythm in response to particulate pollution were originally suggested by two observational studies. Increases in heart rate in nearly 3000 subjects were observed during a pollution episode in Central Europe in January 1985.¹ In a panel study in Utah, pulse rate (and the likelihood of the pulse rate being increased) were positively associated with levels of PM₁₀ on the preceding one to five days.⁵³ An increase in resting heart rate suggests either reduced vagal or increased sympathetic cardiac control and is recognised as an independent risk factor for total cardiovascular mortality and sudden death.^{54–55} The mechanisms by which abnormal autonomic control influence prognosis are not proven, but there is strong animal evidence that increased sympathetic and reduced vagal control results in an increased susceptibility of ischaemic myocardium to ventricular fibrillation.⁵⁶ Thus, these two observational studies provide a plausible link between exposure to particulate pollution and sudden cardiac death in susceptible people.

Experimental animal evidence also supports the hypothesis that the cardiac autonomic nervous system is susceptible to the adverse effects of air pollution. In dogs with partially ligated coronary arteries exposed to concentrated ambient particles through tracheostomy, heart rates rose with increasing PM₁₀ exposure and cardiac autonomic control measured by heart rate variability (HRV) was altered.⁵⁷ Decreased HRV reflects impaired vagal cardiac control and is an independent predictor of cardiac death in patients with established heart disease such as myocardial infarction⁵⁸ and chronic heart failure.⁵⁹ Analysis of ambulatory ECG recording from seven elderly subjects during particulate pollution episodes from a steel mill showed consistent negative

associations between pollution and same day measures of HRV.⁶⁰ In two further groups of elderly patients, the risk of a person having low HRV was significantly increased on high PM_{2.5} days.^{61, 62} In an occupational study, the limitations in estimating personal exposure from regional monitoring were overcome by the use of personal exposure monitors in a cohort of 40 boilermakers. A significant negative association was found between 4 hour PM_{2.5} exposure and 24 hour standard deviation of normal to normal RR intervals, a standard index of HRV.⁶³ Experimental laboratory exposure to sulfur dioxide in humans has also recently been shown to exert significant adverse effects on HRV.⁶⁴

Exactly how inhalation of pollutants and, in particular, fine particles can exert such effects on the cardiac autonomic nervous system remains to be elucidated. Animal work has shown that stimulation of nasopharyngeal, upper, and lower airway receptors can mediate powerful neural influences on the cardiovascular system.⁶⁵ Alternatively, and in keeping with the inflammatory hypothesis, inhaled particles may indirectly promote an autonomic stress response as a result of cytokine release.

These two mechanistic hypotheses in combination may thus explain the observed acute effects of air pollution on cardiovascular morbidity and mortality. In susceptible people, pollution may increase the likelihood of plaque rupture, promote ischaemia, and increase the vulnerability of ischaemic or failing myocardium to lethal arrhythmia (fig 1).⁶⁶

CHRONIC EFFECTS

The long term effects of air pollution exposure on the cardiovascular system are more difficult to determine but a small number of studies has highlighted potentially important associations. Two large prospective cohort studies have found associations between long term exposure to fine PM and cardiopulmonary mortality.^{6, 67} In the US six cities study involving over 8000 subjects, the effects of air pollution on mortality were estimated while controlling for other risk factors. Over a 16 year follow up period, city specific cardiopulmonary mortality rates were found to be associated with the average concentrations of particulate pollutants in each city.⁶ The American Cancer Society found an association between fine particulate and sulfur oxide pollution and cardiopulmonary mortality after a six year follow up in over 500 000 adults. Each 10 µg/m³ increase in fine particulate air pollution was associated with a 6% increase in risk of cardiopulmonary mortality.⁶⁸ Most recently in a study from the Netherlands a consistent association was found between long term exposure to traffic related pollution and cardiopulmonary mortality. Living near a major road and hence being exposed to the highest levels of both black smoke and nitrogen dioxide was associated with a relative risk of cardiopulmonary mortality of 1.95.⁶⁹

The association between long term pollution exposure and cardiovascular death may also be explained by the inflammatory properties of fine particles. In addition to the relation

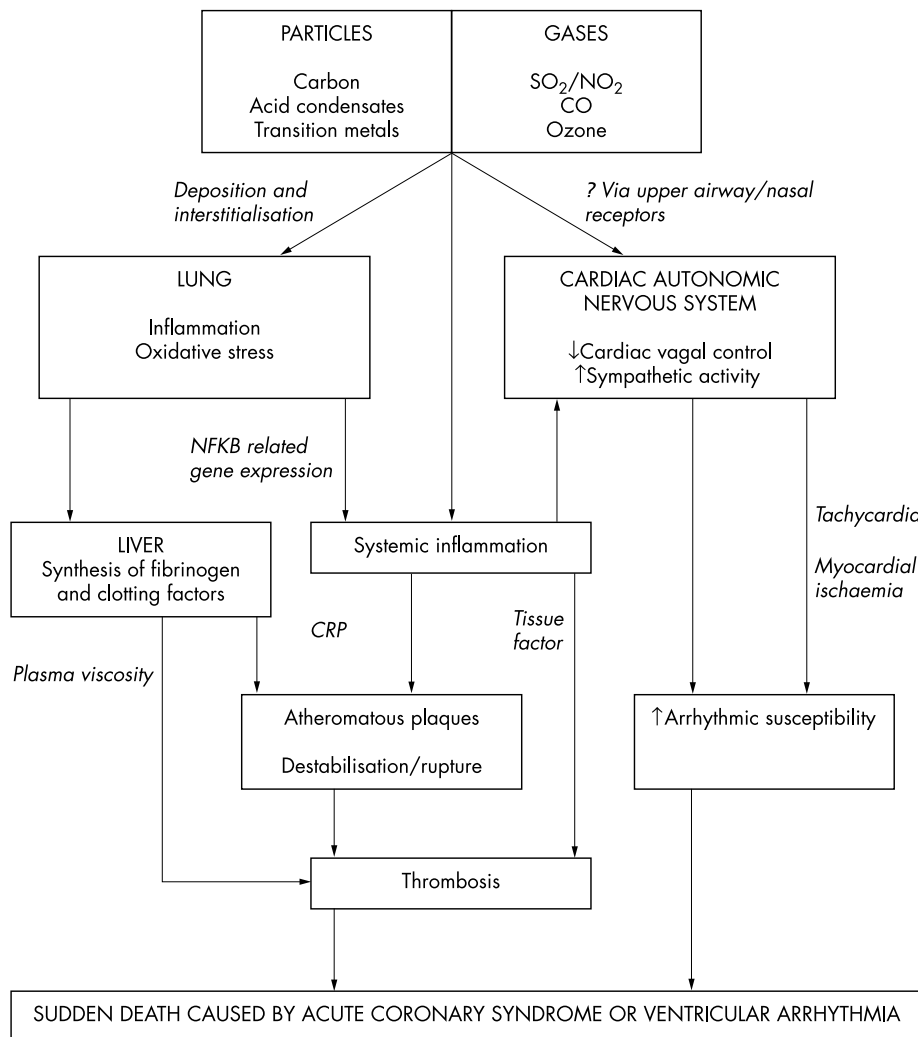


Figure 1 Mechanisms by which particulate and gaseous air pollutants may exert adverse effects on the cardiovascular system.

between acute cardiac events and inflammatory stimuli, there is growing evidence of the importance of inflammation in the atherogenic process itself.⁷⁰ Markers of inflammation such as C reactive protein can predict long term cardiovascular mortality in apparently healthy subjects.³⁷ In patients undergoing diagnostic coronary angiography, serological evidence of multiple exposure to infectious agents is related to the extent of atherosclerosis and to long term prognosis.⁷¹ Although this awaits supportive experimental evidence, one may hypothesise that, in a similar manner to cigarette smoking, repeated exposure to pollutants would contribute to a chronic inflammatory state, increasing the propensity to atherogenesis.

FUTURE RESEARCH

The unpredictable nature of coronary artery disease remains a problem that concerns all cardiologists. Patients with chronic stable angina have a low annual rate of clinical events, but sudden death and acute coronary syndromes including acute myocardial infarction can present without warning both in patients with established disease and in apparently healthy people. Surprisingly little attention has been paid to environmental factors that may influence levels of inflammation and autonomic tone and thus cardiovascular risk. The role of air pollution in determining inflammatory or oxidative status and cardiac autonomic control remains to be determined, but it can be seen that the epidemiological evidence for the association of air pollution with cardiac mortality and morbidity is beyond doubt. Research already underway will throw light upon which components of air pollution are important in these respects and at what levels. The determination of possible threshold effects or "safe" levels will help to establish both appropriate legal standards and the policies required for air quality control. In addition, basic research into exactly how air pollution may result in adverse cardiac events may help to improve our understanding of the triggers of plaque rupture and arrhythmia. Further clinical studies are required but cellular and molecular studies in the field of atherosclerosis and arrhythmia should assess the impact of environmental factors such as air pollution.

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IMAGES IN CARDIOLOGY

Pulmonary artery sarcoma

A 38 year old man without any symptoms was referred to our hospital for examination of a heart murmur. There were signs of right ventricular overload on the ECG. Doppler echocardiographic measurements demonstrated a maximum pressure gradient of 105 mm Hg across the right ventricular outflow tract. Lung perfusion scanning demonstrated reduced tracer uptake in the right lung. Although we initially suspected pulmonary thromboembolism, the computed tomographic angiography revealed severe luminal stenosis and a solid mass arising from the right ventricular outflow tract extending into both left and right pulmonary arteries (see fig), which are atypical findings for pulmonary thromboembolism. The morphological characteristics detected by computed tomography suggested the diagnosis of pulmonary artery sarcoma. After intraoperative pathologic examination of the frozen section confirmed the diagnosis of pulmonary artery sarcoma, radical resection and reconstructive surgery using a cryopreserved homograft were performed. The patient received postoperative radiotherapy and chemotherapy, and

has remained well over the subsequent 10 months.

Pulmonary artery sarcoma is extremely rare and has a poor prognosis. The diagnosis is difficult and often initially misdiagnosed as pulmonary thromboembolism. It has been reported that a mean survival is only 1.5 months after diagnosis without surgical intervention. Early diagnosis and aggressive surgical treatment are the only ways of effecting

a cure. Computed tomography may offer adequate information on the extent of a neoplasm, which helps us to differentiate a pulmonary artery sarcoma from pulmonary thromboembolism.

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