Cardiovascular Effects of Nanoparticles

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Over the past decades epidemiological and toxicological studies have provided a body of evidence that elevated levels of ambient particulate air pollution are associated with increased cardiovascular morbidity and mortality. Various cardiovascular risk factors, i.e. elevated heart rate, decreased heart-rate variability, arterial vasoconstriction, augmented systolic blood pressure, and increased plasma viscosity were associated with ambient particle exposure. These changes may result in detrimental consequences for cardiac function, especially in patients with ischemic heart disease, cardiac arrhythmias, and congestive heart failure. Related to those findings, recent toxicological studies have put special emphasis on adverse effects mediated by nanoparticles, the environmental source of which are primarily traffic related combustion processes. With increasing commercial interest in nanoparticles or nanotubes, the risks associated with occupational exposure will become a matter of concern. Recent investigations provide evidence that nanoparticles can be quickly translocated from the lungs into the circulation and to secondary target organs, such as liver, heart, spleen, and brain. Therefore, the following mechanisms mediating cardiovascular effects of inhaled nanoparticles are postulated: (A) pulmonary and/or systemic inflammatory responses leading to endothelial dysfunction and a pro-coagulatory state, (B) direct interactions of translocated nanoparticles with endothelium and/or blood constituents promoting thrombogenesis, (C) dysfunction of the autonomic nervous system mediated by direct reflexes from intrapulmonary receptors and/or by local or systemic inflammatory stimuli, (D) cardiac malfunction due to ischemic responses in the myocardium and/or altered ion-channel functions in myocardial cells. Available data from experimental particle instillations and in-vitro studies are supportive of hypothesis (A) and give evidence for inflammation-mediated enhanced thrombus formation and aggravation of atherosclerotic lesions. In a study designed to specifically address hypothesis (B), we were recently able to demonstrate that intra-arterial application of
nanoparticles significantly enhances platelet accumulation on the venular endothelium of healthy mice. Particle-induced platelet adhesion was strongly associated with deposition of fibrin and increased expression of von-Willebrand factor on the endothelial surface. Inflammatory parameters were not elevated, indicating that nanoparticles may have the potential to exert a pro-thrombotic effect in the vascular system without triggering inflammatory processes. To examine the hypothetical pathway (C) – dysfunction of the autonomic nervous system in response to nanoparticle inhalation – heart rate and heart-rate variability were studied in rats during a 24h exposure to carbonaceous nanoparticles. A mild but consistent increase in heart rate with a significant associated decrease in heart-rate variability was observed. These results point to a particle-induced alteration of cardiac autonomic balance, which is mediated by a sympathetic stress response. In summary, the current toxicological evidence is clearly supportive of adverse cardiovascular effects arising from nanoparticle exposure, but the available data are as yet too scarce to provide a comprehensive understanding of the different pathophysiological pathways involved.

References


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Size effect of intratracheally instilled particles on pulmonary inflammation and vascular thrombosis

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Ultrafine Particles Exert Prothrombotic but Not Inflammatory Effects on the Hepatic Microcirculation in Healthy Mice In Vivo

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Cardiovascular Effects of Nanoparticles

Potential pathophysiological pathways associated with nanoparticle exposure

Lung

Epithelium

Interstitial space

Endothelium

Blood vessel

Systemic effects mediated by

Autonomic nervous system

Translocation of particles

Inflammatory signals

Heart

Ischemia

Arrhythmia

Liver

Acute phase response

Prothrombotic factors

(Micro)vascular system

Endothelial dysfunction

Thrombosis

Atherosclerosis
Effects on the Autonomic Nervous System

Do inhaled nanoparticles alter the autonomic balance?

Parameters:
- Heart Rate
- Heart Rate Variability

Particles

Afferent Lung Receptors

Medullary Centers

Symp

Vagal

Blood Vessels

Heart

(+)

(-)

(-)

(+)

(+)

GSF-National Research Center for Environment and Health

IHB-Institute for Inhalation Biology
Experimental Approach – Telemetric Measurement of Heart Rate and Heart Rate Variability

**Clean air**

**np-CB**

**Exposure for 24h**

Carbon black
Spark discharging
38 nm
180 µg·m⁻³
1.6 \(10^7\) cm⁻³

**Baseline**

**Exposure**

**Recovery**

Heart rate: RR-Intervall
Heart rate variability:
Ttime domain: SDNN

Exposure to Carbon Black via Spark Discharging

Baseline Exposure Recovery

Carbon black
Spark discharging
38 nm
180 µg·m⁻³
1.6 \(10^7\) cm⁻³

**Heart rate:** RR-Intervall

**Heart rate variability:**

Ttime domain: SDNN

Electrocardiogram

mV

0,0
0,5
1,0

R

R

R
Increased heart rate and reduced heart rate variability during exposure suggest a sympathetic stress response.
Is the stress response associated with pulmonary inflammation?

The dissociation between cardiac and inflammatory responses and the lack of a systemic acute phase reaction suggest a neural pathway for cardiac stress response via activation of receptors in the lungs.

Acute phase reactants and coagulation parameters are not altered.
Do systemically available nanoparticles exert inflammatory and/or prothrombotic effects in the vascular system?

Experimental approach - C57BL/6J-mice
- Intraarterial application of nanoparticles (Printex 90)
- Solely mimicking effects of translocated particles
- Excluding effects of inflammatory signals from the lungs
- Intravital video-fluorescence microscopy of hepatic microcirculation:
  Leucocyte-platelet-endothelial cell interactions
Leucocyte-Platelet-Endothelial Cell Interactions

Fibrinogen

Blood vessel

Rolling
Adhesion
Migration

Extracellular Matrix

von Willebrand Factor
Leucocyte-Endothelial Cell Interactions in Hepatic Microvessels

No effects on rolling and adhesion of leucocytes in postsinusoidal venules
Platelet-Endothelial Cell Interactions in Hepatic Microvessels

**Rolling Platelets**

[1/mm/sec]

- **arterioles**
- **venules**

mean +/- SEM, n = 6, n.s.

**Adherent Platelets**

[1/mm²]

mean +/- SEM, n = 6

*p < 0.05 vs. control

Glycoprotein IIb/IIIa inhibition by Tirofiban

Increased numbers of adherent platelets in microvessels

Khandoga et al. 2004
Deposition of Alexa 488 conjugated fibrin(ogen)

Plasma concentrations
Sham 746 ± 219 µg/ml
nP-CB 1493 ± 256 µg/ml, p = 0.093

Immunostaining for fibrin(ogen)

Immunostaining for vWF

Khandoga et al. 2004
Microvascular Effects of „Translocated“ Nanoparticles

• No effects on
  - sinusoidal perfusion
  - leucocyte-endothelial cell interactions
  - microvascular permeability
  - (fibrinogen plasma level)

• Induction of GPIIb/IIIa-mediated platelet adhesion

• Deposition of fibrin(ogen) and increased expression of vWF in microvessels

➢ Ultrafine particles exert prothrombotic but not inflammatory effects on the hepatic microcirculation in vivo

Khandoga et al. 2004
On-Road Exposure of Aged Rats to Highway Aerosols

Exposure
Highway aerosol
Truck - 6-h driving period
Mainly nanoparticles:
1 – 3 x 10^5 cm^-3

Endothelins help to regulate normal cardiovascular homeostasis between vasoconstriction and vasodilation.

Increased plasma levels of ET-1 and ET-3 after nanoparticle exposure suggest endothelial dysfunction. Elevation of ET-3 was found to be associated with systemic vasoconstriction in cardiac patients.

Elder et al. 2004

Increased plasma levels of ET-1 and ET-3 after nanoparticle exposure suggest endothelial dysfunction. Elevation of ET-3 was found to be associated with systemic vasoconstriction in cardiac patients.
Ultrafine Particles Affect Experimental Peripheral Thrombosis in an In Vivo Hamster Model

Intravenous Application of Polystyrene Nanoparticles (60 nm)

- Instillation of polystyrene NP
- unmodified
- negatively charged (carboxylate-modified)
- positively charged (amine-modified)
The lack of a clear association between PMN influx and thrombosis suggests that pulmonary inflammation in itself is not the primary cause for the augmented peripheral thrombosis.

Further studies show that platelets are also activated by translocated nanoparticles in this experimental setting.
Current experimental evidence supports an association between nanoparticle exposure and adverse cardiovascular outcomes.

Underlying pathophysiological pathways are:
- alteration of the autonomic cardiac control, most likely mediated via neural reflexes from peripheral lung receptors,
- induction of a pro-thrombotic situation and endothelial dysfunction caused by translocated particles.

Inflammatory responses in the lung appear not to be the primary cause for cardiovascular effects.

More studies are clearly needed to substantiate our current understanding of the pathophysiological links between nanoparticle exposure and adverse cardiovascular outcomes.