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Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate editor: J. Fedan

The heart as an extravascular target of endothelin-1 in particulate matter-induced cardiac dysfunction

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ARTICLE INFO

Keywords:

Cardiac dysfunction
 Particulate matter
 Air pollution
 Endothelin-1
 Heart
 Autocrine/paracrine signaling

ABSTRACT

Exposure to particulate matter air pollution has been causally linked to cardiovascular disease in humans. Several broad and overlapping hypotheses describing the biological mechanisms by which particulate matter exposure leads to cardiovascular disease have been explored, although linkage with specific factors or genes remains limited. These hypotheses may or may not also lead to particulate matter-induced cardiac dysfunction. Evidence pointing to autocrine/paracrine signaling systems as modulators of cardiac dysfunction has increased interest in the emerging role of endothelins as mediators of cardiac function following particulate matter exposure. Endothelin-1, a well-described small peptide expressed in the pulmonary and cardiovascular systems, is best known for its ability to constrict blood vessels, although it can also induce extravascular effects. Research on the role of endothelins in the context of air pollution has largely focused on vascular effects, with limited investigation of responses resulting from the direct effects of endothelins on cardiac tissue. This represents a significant knowledge gap in air pollution health effects research, given the abundance of endothelin receptors found on cardiac tissue and the ability of endothelin-1 to modulate cardiac contractility, heart rate, and rhythm. The plausibility of endothelin-1 as a mediator of particulate matter-induced cardiac dysfunction is further supported by the therapeutic utility of certain endothelin receptor antagonists. The present review examines the possibility that endothelin-1 release caused by exposure to PM directly modulates extravascular effects on the heart, deleteriously altering cardiac function.

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Abbreviations: ACSCP II, American Cancer Society Cancer Prevention II; ANS, autonomic nervous system; BP, blood pressure; CV, cardiovascular; CVD, cardiovascular disease; CS, cigarette smoke; CAP, concentrated ambient particle; CHF, congestive heart failure; COX, cyclooxygenase; DE, diesel exhaust; eNOS, endothelial NO synthase; ET, endothelin; ETR, endothelin receptor; ET_AR, endothelin receptor A; ET_BR, endothelin receptor B; EPA, Environmental Protection Agency; FA, filtered air; HF, heart failure; HR, heart rate; HRV, heart rate variability; MAP, mean arterial pressure; MESA, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction; NO, nitric oxide; NO₂, nitrogen dioxide; O₃, ozone; PM, particulate matter; PGI₂, prostacyclin; PAH, pulmonary arterial hypertension; SHR, spontaneously hypertensive rat; SO₂, sulfur dioxide; TXA₂, thromboxane A₂; TRPA1, transient receptor potential cation channel member A1; UF, ultrafine; UFP, ultrafine particle; US, United States; Zn, zinc.

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<http://dx.doi.org/10.1016/j.pharmthera.2016.05.006>
 0163-7258/Published by Elsevier Inc.

Please cite this article as: Chan, E.A.W., et al., The heart as an extravascular target of endothelin-1 in particulate matter-induced cardiac dysfunction, *Pharmacology & Therapeutics* (2016), <http://dx.doi.org/10.1016/j.pharmthera.2016.05.006>

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1. Introduction

Cardiovascular disease (CVD) encompasses many pathologies of the blood vessels and/or the heart. CVD includes stroke, coronary artery diseases (such as angina and heart attacks), hypertension, atherosclerosis, and cardiac dysfunction. CVD is the leading cause of mortality, causing one out of four deaths in the United States (US) (CDC, 2015) and ~30% of deaths (~17.5 million people in 2012) worldwide (WHO, 2014a).

2. Particulate matter exposure and cardiovascular disease

2.1. Particulate matter air pollution

Of the 17.5 million CVD-related deaths in 2012, ~3 million were associated with exposure to ambient air pollution (WHO, 2014a, 2014b). Ambient air contains a complex mixture of particulate matter (PM), gases (e.g., nitrogen dioxide [NO₂], carbon monoxide, sulfur dioxide [SO₂], ozone [O₃]), semivolatile and volatile organics, and other pollutants, which can vary by source, location, time of day, and season. Although PM is derived in part from natural sources such as pollen dust and volcanic ash, anthropogenic sources including motor vehicle emissions and power plants are the major sources of concern, as PM released from these sources is thought to contain high levels of pro-oxidant organics (e.g., polyaromatic hydrocarbons) and transition metals (e.g., iron, nickel, vanadium).

PM varies by size, solubility, particle number, atmospheric/biological stability, source, and charge, which may all be determinants of toxicity potential. The smaller the particle, the higher the surface area-to-mass ratio and the greater the potential for adsorption of substances (e.g., metals, endotoxin, or organic compounds) that can modulate the biological effects and/or toxicity of PM (US EPA, 2009). PM has long since been recognized as a threat to human health, with the US Environmental Protection Agency (EPA) promulgating both short-term (24 h) and long-term (annual) National Ambient Air Quality Standards since 1971 (36 FR 8186).

PM is heterogeneous in size and is commonly described by nominal aerodynamic diameter in microns (μm). Whereas the diameter of a human hair is approximately 100 μm and the limit of human vision is about 50 μm, coarse particles (PM₁₀) are ≤10 μm in diameter, fine particles (PM_{2.5}) are ≤2.5 μm and ultrafine particles (UFPs) have a diameter of ≤0.1 μm (WHO, 2003; Brook et al., 2004). In humans, the site and amount of PM deposition are highly influenced by inhalation route (nasal vs. oronasal) and inhaled particle size fraction (Brown et al., 2013). Generally, nasal inhalation is associated with reduced particle penetration into the lower respiratory tract. With regard to particle size fractions, UFP and PM_{2.5} deposit throughout the respiratory tract, whereas coarse particles (nominal mean particle size between 2.5 and 10 μm) largely deposit in the upper respiratory tract and to a lesser extent in the lungs (US EPA, 2009).

2.2. Air pollution and cardiovascular disease

Multiple lines of evidence over the last several decades have demonstrated associations between PM exposure and CVD, and in 2009 the US EPA determined that a causal relationship exists between short- and long-term exposures to PM_{2.5} and cardiovascular (CV) effects in humans (US EPA, 2009).

2.2.1. Mortality

Evidence of a relationship between ambient air pollution and adverse human health consequences date back to the early 1900s. One of the first documented events demonstrating that air pollution was directly associated with morbidity and mortality occurred in December 1932, when a thick fog covered an industrialized region of Belgium for five days and 60 people died (Nemery et al., 2001). Twenty years later a similar event caused the London Smog of 1952, in which daily average PM concentrations reached >4 mg/m³ (Scott, 1953). Up to 12,000 deaths were attributed to this smog event (Bell et al., 2004).

The initial realization that exposure to polluted air was associated with increased mortality has been supported by multiple long-term prospective air pollution studies. The Harvard Six Cities Study evaluated >8000 subjects and showed an association between air pollution (estimated using a single outdoor monitor at each location) and mortality due to lung cancer and cardiopulmonary disease (Dockery et al., 1993). Two years later an analysis of the American Cancer Society Cancer Prevention II (ACSCPII) cohort presented similar findings from >500,000 individuals residing in all US states (Pope et al., 1995). Specifically, ambient PM_{2.5} and sulfate particulate air pollution were associated with all-cause, cardiopulmonary, and lung cancer mortality. Deaths in the ACSCPII cohort were related to ischemic disease, arrhythmias, heart failure (HF), and myocardial infarction (MI). Follow-up and reanalysis of both studies have strengthened the original conclusions (Krewski et al., 2005a, 2005b; Laden et al., 2006; Turner et al., 2011; Lepeule et al., 2012; Jerrett et al., 2013; Pope et al., 2015).

One of the largest (>2 million Canadian subjects) studies of chronic PM exposure to date found an association between PM_{2.5} and mortality in a retrospective cohort (Crouse et al., 2012). This finding was especially compelling as the association was observed with exposures to relatively low estimated mean PM_{2.5} concentrations (mean, 8.7 μg/m³; interquartile range, 6.2 μg/m³). Although the relative risk of ambient air pollution was small, a meta-analysis of 11 long-term air pollution exposure and mortality publications found a pooled effect estimate of 6% (95% CI: 4, 8%) for all-cause and 11% (95% CI: 5, 16%) for CV mortality, per 10 μg/m³ increase in PM_{2.5} exposure (Hoek et al., 2013). As nearly everyone is exposed to air pollution, even a small relative risk equates to a large number of individuals that will develop CVD from exposure to air pollution.

A large body of peer-reviewed literature that chronicled the effects of short-term exposure (<1 week) has used time-series analyses to provide strong supporting evidence connecting PM to morbidity and mortality. The National Morbidity, Mortality, and Air Pollution Study was performed in 100 cities in the US and observed PM exposure-related mortality (Peng et al., 2005). Regarding PM₁₀, a study of 16 cities in China with relatively high concentrations (52 to 156 μg/m³) found associations with CV and respiratory mortality (Chen et al., 2012a). In the same study, females, people over the age of 64, and residents with less education appeared to be at increased risk of health effects caused by PM₁₀ exposure, suggesting that PM air pollution can also exacerbate CV disease in at-risk populations. Relatively low PM_{2.5} levels in the Greater Boston area were associated with ischemic stroke, with an increase of just 6.4 μg/m³ PM_{2.5} elevating the odds ratio by 1.11 (95% CI: 1.03–1.20) (Wellenius et al., 2012).

2.2.2. Vascular disease and atherosclerosis

Findings from the large Multi-Ethnic Study of Atherosclerosis (MESA) and Framingham cohorts have shown that chronic exposure to low levels of PM was associated with vasoconstriction and

endothelial dysfunction (Krishnan et al., 2012; Wilker et al., 2014). Long-term PM_{2.5} exposure in the MESA cohort members was also associated with arterial wall thickening and the development of systemic atherosclerosis, with a 5 µm/year increase in carotid intima-media thickness for each 2.5 µg/m³ increase in PM_{2.5} (Adar et al., 2013). These findings are in agreement with studies of increased carotid intima-media thickness in elderly men in Boston (Wilker et al., 2013) and adults in Spain (Rivera et al., 2013) exposed to varying levels of traffic-related PM.

2.2.3. Heart failure

Changes in activity level require rapid increases and decreases in cardiac output to maintain a sufficient supply of oxygenated blood. HF occurs when the heart is unable to pump sufficient amounts of blood to meet the oxygenation needs of the body, and was the leading cause of Medicare-funded hospitalizations in 2010 (Pfunter et al., 2013). HF can be chronic and, when accompanied by edema, congestive. Congestive HF occurs when fluid moves out of the vasculature more quickly than it can be returned by the lymphatic system, due to an increase of pressure in the veins resulting from low cardiac output (Cho & Atwood, 2002).

The ACSPII cohort is one of the few that assessed HF mortality, finding an association with long-term PM_{2.5} exposure (Pope et al., 2004). Short-term exposure to PM has also been linked to HF hospitalizations. Hospital admission records from 11.5 million Medicare enrollees living near (average distance of 6 miles) a PM_{2.5} monitor experienced a 1.28% (95% CI: 0.78–1.7895%) increase in HF-related hospital admission per 10 µg/m³ increase in PM_{2.5}, the largest increase found in the study (Dominici et al., 2006). Interestingly, higher exposure to traffic-related air pollution was associated with an increased mortality rate in those with HF (Medina-Ramon et al., 2008). In agreement, a reduction in PM_{2.5} exposure was associated with a decrease in HF hospitalizations (Dominici et al., 2006). Finally, a meta-analysis of short-term air pollution exposure found for every 10 µg/m³ increase in PM_{2.5} there was a 2.12% (95% CI: 1.42–2.82%) increase in HF hospitalization or death (Shah et al., 2013).

2.2.4. Heart rate variability

Heart rate variability (HRV) has been a useful health outcome measured in response to both short- and long-term exposure to air pollution. HRV is a measure of the variability in the time between heart beats and an indirect indicator of autonomic tone, making it a valuable prognostic indicator of CV well-being (Task Force of the European Society of Cardiology, 1996). Decreased HRV denotes a shift toward increased sympathetic tone and can be used as a biomarker of increased risk for CV morbidity and mortality.

A recent meta-analysis of 29 epidemiologic studies evaluated the relationship between HRV and short-term air pollution exposure (Pieters et al., 2012). The report concluded that multiple measures of HRV were consistently inversely associated with PM_{2.5} air pollution exposure. In addition, controlled human exposure studies have shown that the timing of reductions in HRV occur quickly, within minutes to hours of air pollution exposure (Brook et al., 2010, 2014), potentially providing insight into the mechanism behind this change.

2.3. Mechanisms of particulate matter exposure-induced cardiovascular dysfunction

As the body of literature connecting PM air pollution to CVD continues to grow, so does interest in the biological mechanisms involved. An understanding of the mechanisms behind PM-induced CVD at all biologic levels, including molecular, cellular, tissue, and organ, could provide biologic plausibility for the epidemiological findings and thus guide air quality policies and decision making.

Three broad and potentially overlapping mechanisms have been proposed to explain how PM inhalation may lead to overt, subacute,

subchronic, and chronic responses in the CV system (Franklin et al., 2015). These pathways are: (1) pulmonary/systemic inflammation and oxidative stress, (2) autonomic nervous system (ANS) dysregulation/imbalance, and (3) translocation/absorption of PM and/or its components into the bloodstream and transport to other areas of the body. Though each pathway is associated with certain CV outcomes and occurs over a different time frame, there is likely significant cross-talk between the pathways. For example, the ANS can signal through adrenergic receptors on immune cells to mediate inflammation (Bellinger & Lorton, 2014; Forsythe, 2015).

Many PM constituents (e.g., metals and quinones) have been shown to generate reactive oxygen species, capable of causing oxidative stress (Kelly, 2003; Li et al., 2008; Jeng, 2010; Moller et al., 2010). Additionally, PM can increase pulmonary (Hao et al., 2003; Li et al., 2010; Jin et al., 2011) and systemic (Fujii et al., 2002; van Eeden & Hogg, 2002; Zhao et al., 2013) proinflammatory cytokine levels, including C-reactive protein, tumor necrosis factor-α, and interleukin-6 (Brook et al., 2010). Following alveolar macrophage and/or dendritic cell uptake of PM, cytokine release by phagocytic cells can stimulate bone marrow production of white blood cells, such as neutrophils and leukocytes (Bouthillier et al., 1998; Hiura et al., 1999; Fujii et al., 2002; van Eeden & Hogg, 2002; Hiraiwa & van Eeden, 2013). Regarding timing, PM-induced inflammation typically occurs hours to days after exposure (Delfino et al., 2008). Local inflammatory responses in the lung can then 'spill over' into the circulation, causing systemic oxidative stress and inflammation characterized by an increase in activated white blood cells, platelets, and cytokine expression. Systemic inflammation can then lead to vasoconstriction, increased thrombogenicity and coagulation, endothelial injury, and later atherosclerotic plaque progression, coronary vasospasm, and myocardial ischemia (Brook et al., 2010).

The ANS is involved in the involuntary control of functions such as HR, which must quickly adjust in response to activity level changes. ANS activation may account for many changes in cardiac function occurring after PM exposure, such as HR, blood pressure (BP), and cardiac arrhythmias. ANS-mediated changes can occur within seconds of activation, potentially accounting for the near-immediate (0–4 h) manifestation of certain CV effects (Peters et al., 2001; Peretz et al., 2008; Brook et al., 2009). Air pollution exposure may modulate the ANS through the activation of sensory afferent nerves that are triggered by the nociceptive transient receptor potential cation channel member A1 (TRPA1), an ion channel found on the surface of many nerves and other cells in the respiratory tract. When activated, TRPA1 can mediate ANS imbalance and CVD (Ghelfi et al., 2008). For example, exposure to diesel exhaust (DE), a mixture of air pollutants including PM, increased the sensitivity of rat hearts to triggered arrhythmias, which was abrogated upon TRPA1 signaling blockade (Hazari et al., 2011).

PM and/or its constituents may also translocate directly to sites of CV dysfunction, such as the heart. Several animal studies provide evidence that PM and/or soluble particle constituents translocate into, directly interact with, and impact CV tissues (Takenaka et al., 2001; Kreyling et al., 2002; Furuyama et al., 2009). This pathway may also mediate systemic inflammation, as PM could initiate local inflammation/oxidative stress after extrapulmonary translocation.

2.4. An emerging mechanism of cardiac dysfunction

In this review, we propose that altered autocrine/paracrine signaling, specifically that of the endothelin (ET) system, is a direct cause of cardiac dysfunction following PM exposure. While there may be several autocrine/paracrine agents involved in the spectrum of cardiac dysfunction associated with PM exposure, ET is a likely candidate as the ET system is activated in the pulmonary and CV systems following PM exposure (Levin, 1995; Finch & Conklin, 2015). In addition, ETs mediate several cardiac responses, and thus may be a key mediator of cardiac dysfunction following PM exposure.

3. Particulate matter air pollution and endothelin production

3.1. The endothelin system

The ET system is composed of at least four ET isoforms (Inoue et al., 1989a) and at least two ET receptors (ETR) (Masaki et al., 1994). ET signaling is primarily known for inducing vasoconstrictive effects (Levin, 1995), which can be countered by nitric oxide (NO) (Palmer et al., 1987). In addition to vessel constriction, ETs can also mediate several physiological functions outside of the vasculature, such as within the heart.

3.1.1. Endothelin-1

Of the ET isoforms, ET-1 is the most abundant in the human CV system and exerts the greatest vasoconstrictive effects (Luscher & Barton, 2000; Kedzierski & Yanagisawa, 2001). In addition to being the most potent and long-lasting vasoconstrictive peptide currently known (Yanagisawa et al., 1988a, 1988b), ET-1 is also involved in development (Clouthier et al., 2000; Kedzierski & Yanagisawa, 2001), immune system regulation (Nett et al., 2006), glucose sensitivity (Lteif et al., 2007), kidney function (Kohan, 2006), brain function (Kedzierski & Yanagisawa, 2001), and cardiac function (Brutsaert, 2003). The majority of ET-1 is released by vascular endothelial cells, although expression level can be modulated by stretch, shear stress, hypoxia, and the presence of factors such as NO (Inoue et al., 1989a, 1989b; Yoshimoto et al., 1991; Malek et al., 1999; Kedzierski & Yanagisawa, 2001). Expression can also be induced in smooth muscle (Hahn et al., 1990), macrophages (Ehrenreich et al., 1990), fibroblasts, neurons (Luscher & Barton, 2000; Kedzierski & Yanagisawa, 2001), and cardiomyocytes (Ito et al., 1993).

Several lines of evidence suggest that ET-1 functions as an autocrine/paracrine regulator of smooth muscle cells, as opposed to a circulating agent. Biologically active ET-1 levels within the vascular walls can be more than 100-times greater than typically present in human serum (~1–2 pg/ml) (Shaw et al., 2000; Kedzierski & Yanagisawa, 2001). In addition, the half-life of ET-1 is only about 1 min (Gasic et al., 1992), likely preventing effects at locations distant from the site of production. Although ET-1 is rapidly cleared, the resulting constrictive effects can last for hours to days (Asano et al., 1989; Vierhapper et al., 1990).

3.1.2. Endothelin receptors

Endothelin receptors A (ET_AR) and B (ET_BR) are G-protein coupled receptors that initiate intracellular signaling cascades upon activation (Bremnes et al., 2000). After ligand binding, Ca²⁺ signaling is increased in target cells via pathways involving phospholipase C stimulation (Resink et al., 1988). ET-1-mediated Ca²⁺ influx can be long-lasting (>20 min) (Simonson et al., 1989; Simonson & Dunn, 1990a) and so great that Ca²⁺ flowing through gap junctions is sufficient to initiate Ca²⁺ signaling in adjoining cells unbound by ET-1 (Simonson & Dunn, 1990b).

Many cell types express both ETRs, and the ratio of one to the other can vary (Kedzierski & Yanagisawa, 2001). ET_ARs expressed on vascular smooth muscle cells mediate vasoconstriction. On the other hand, ET_BR, the sole ETR found on endothelial and renal collecting-duct cells (Johnstrom et al., 2005), function in ET clearance and in the release of vasodilators such as NO (Verhaar et al., 1998). As such, ET-1 injection into the vasculature causes a brief vessel relaxation due to ET_BR activation. However this effect is quickly reversed by ET-1 binding to ET_AR, which reduces NO production in vascular smooth muscle cells and leads to the well-known constrictive effects of ET-1 in the vasculature.

3.1.3. The endothelin system in the heart

ET-1 can be produced by, and exert extravascular effects on, various cell types within the heart. Cardiomyocytes, endocardial/myocardial endothelial cells, and cardiac fibroblasts can release ET-1, whereas both ET_AR and ET_BR are expressed on cardiomyocytes, fibroblasts,

smooth muscle cells, and endocardial/myocardial endothelial cells (Yanagisawa et al., 1988b; Sakai et al., 1996; Gray et al., 1998). Activation of ET_AR signaling within cardiomyocytes can alter the force of myocardial contraction (inotropy) (Li et al., 1991; Mebazaa et al., 1993), heart rate (chronotropy) (Kedzierski & Yanagisawa, 2001), hypertrophy (Ito et al., 1993), and cardiac rhythmicity (Russell & Molenaar, 2000). Approximately 90% of the ETRs on cardiomyocytes are ET_AR (Fareh et al., 1996; Modesti et al., 1999), suggesting that the functional role of the ET system within the heart may be biased toward downstream effects of ET_AR. Thus ET production by multiple cell types in the heart combined with high ET_AR expression by cardiomyocytes could set the stage for ET-mediated cardiac dysfunction.

3.2. Endothelin-1 and cardiovascular disease

Endothelial dysfunction, the imbalanced release of vasoactive mediators, has been strongly associated with CV events. In healthy individuals ET and NO production are balanced to maintain normal vascular tone (Haynes & Webb, 1994). However, aberrant ET-1 mediated effects can lead to CVD, such as ischemia, hypertension, atherosclerosis, and cardiac dysfunction.

3.2.1. Ischemia and myocardial infarction

Ischemia, or inadequate supply of blood to a tissue or organ, can lead to MI when occurring within the heart. The ET system plays an important role in the consequences of ischemia and MI (Cernacek et al., 2003). Myocardial ischemia activates the ET system, upregulating ET-1 peptide levels and ETR transcription (Cernacek et al., 2003). Correspondingly, short-term inhibition of ET signaling in animal models immediately post-infarction improved survival rate and cardiac function. In humans, the levels of circulating ET-1 peptide were eight- and five-fold higher within a few hours of MI that did or did not cause reversible damage to the heart, respectively (Stewart et al., 1991).

3.2.2. Hypertension

The potential role of ET-1 in hypertension, an increase in mean arterial pressure (MAP; cardiac output multiplied by systemic vascular resistance), was postulated soon after its discovery. Bolus injection of ET-1 caused an immediate, but brief (minutes), increase in vessel diameter (Wright & Fozard, 1988) due to ET_BR-mediated NO release (Filep et al., 1993). This was quickly countered by ET activation of ET_ARs, which mediate strong and long-lasting vessel constriction. An increase in vascular resistance without a concurrent decrease in cardiac output can set the stage for hypertension by increasing MAP, and thus systemic BP (Haynes et al., 1991; McMahon et al., 1991; Gasic et al., 1992; Bird et al., 1993; Veniant et al., 1994; Haynes et al., 1996). Interestingly, human pulmonary hypertension is one of the few diseases in which ETR pharmacological agents have improved clinical outcomes.

3.2.3. Atherosclerosis

ET effects have also been linked to atherosclerosis (Ross, 1999), plaque formation in the arteries resulting from a process involving vascular injury, endothelial cell activation, and inflammation. Plaque disruption can release thrombi, leading to ischemic events after lodging in arteries. ET signaling through ET_AR can induce atherosclerosis via the release of proinflammatory mediators (Ruetten & Thiemermann, 1997) and the proliferation of fibroblasts and smooth muscle cells (MacNulty et al., 1990; Fujitani et al., 1995). In turn, ET-1 synthesis is upregulated in endothelial cells and macrophages upon exposure to pro-atherogenic factors (Martin-Nizard et al., 1991; Boulanger et al., 1992). In addition, ET-1 concentrations are increased in the plaques of atherosclerosis in animal models (Mitani et al., 2000) and ET-1 may promote atherosclerosis (Saleh et al., 2010) through its proliferative effects (Luscher et al., 1993). There is also evidence that ET-1-mediated vessel constriction is enhanced in patients with atherosclerosis (Bohm et al., 2002), further exacerbating blood flow obstruction. Moreover, long-

term ET_AR antagonism in humans can attenuate the progression of atherosclerotic coronary plaques (Yoon et al., 2013).

3.2.4. Cardiac hypertrophy

Cardiac hypertrophy, an increase in cardiomyocyte size, commonly occurs in response to hemodynamic stress, and has been related to conditions such as hypertension, HF, and ischemic disease (Frey et al., 2004). Convincingly, the use of an ETR antagonist can attenuate cardiac hypertrophy in rats (Mulder et al., 1997). In addition, ET-1 can initiate several pro-hypertrophic signaling pathways following activation of ET_AR in the heart. For example, ET-1 binding was found to alter Na⁺/H⁺ and Na⁺/Ca²⁺ ion exchangers in rat cardiomyocytes (Dulce et al., 2006). ET_AR signaling can also activate phospholipase C and ERK1/2-mediated transcription of early genes related to hypertrophy (Marshall et al., 2010). Finally, ET may contribute to hypertrophy by mediating the vascular remodeling of resistance arteries (Mulder et al., 1997; Amiri et al., 2004).

3.2.5. Congestive heart failure

Nonphysiological cardiac hypertrophy is often a step on the path toward congestive heart failure (CHF). In support of a role for ET-1 in CHF, ET-1 peptide and ET_BR mRNA expression are increased in the cardiac tissues of patients with CHF (McMurray et al., 1992; Zolk et al., 1999). Concordantly, long-term treatment with an ET_AR antagonist can increase the survival rate of rats with CHF (Sakai et al., 1996). However, human clinical trials of ET_AR antagonists have repeatedly failed to improve the outcomes of patients with CHF (Mylona & Cleland, 1999; O'Connor et al., 2003; Anand et al., 2004; Battistini et al., 2006). Additional research into the mechanistic relationship between ET-1 and CHF may help provide an explanation for this apparent paradox.

3.2.6. Arrhythmia

Cardiac arrhythmia, or irregular heartbeat, can be benign or associated with a variety of adverse health outcomes, from dizziness to cardiac arrest. Ischemic events can cause arrhythmia, however evidence has pointed to a relationship between ET-1 and arrhythmia that does not require ischemia. Direct arrhythmogenic effects of ET-1 were reported in a study in which multiple concentrations of ET-1 (0.1–1 µg/kg) were administered into the aorta, near the coronary ostia of anesthetized rats (Yorikane & Koike, 1990). ET-1 administration had arrhythmogenic effects, even when ischemic effects were absent. The observation that ET-1-induced arrhythmias could occur without concomitant ischemia has since been corroborated by two additional studies in canines (Becker et al., 2000; Szabo et al., 2000).

The mechanism behind direct ET-1-mediated arrhythmia may involve signal re-entry within the heart, ultimately driving action potential duration dispersion (early after depolarizations) and general electrophysiological heterogeneity (Duru et al., 2001). This could be explained, at least in part, by the ability of ET-1 to influence Ca²⁺ handling and K⁺ currents. Along these lines, there is also evidence that prolonged conditions of elevated ET-1 may promote cardiac arrhythmia (Liu et al., 2013). Sub-chronic (2 weeks) administration of ET-1 to rabbits resulted in altered cardiac action potential durations and membrane repolarization after hearts were isolated and perfused. Taken together, it appears that ET-1 directly mediates arrhythmia, although more work remains to better separate the direct arrhythmogenic actions of ET-1 from arrhythmia secondary to ischemia caused by ET-1.

3.3. Particulate matter-induced endothelin system activation

Animal studies first showed that inhalation of PM increased circulating ET-1 levels in 1998 (Bouthillier et al., 1998). Since then a relatively small number of studies have evaluated ET-1 production following PM exposure in humans. Most, but not all, of the human and animal studies have found that PM exposure increased ET-1 levels.

Three studies examined changes in circulating ET-1 peptide level after voluntary human exposure to relatively low concentrations of PM. In one study, ten subjects completed four cycles of 15 min rest and 15 min exercise while being exposed to filtered air (FA) or DE containing 100 µg/m³ PM (Lund et al., 2009). ET-1 peptide levels began to increase within 30 min post-exposure, and were significantly greater 24 h post-exposure. A separate study also demonstrated an effect of DE on ET-1. Exposure to DE containing 200 µg/m³ of PM increased circulating ET-1 levels 3 h after 22 resting subjects completed a two hour-long exposure, whereas no changes were observed in subjects exposed to FA (Peretz et al., 2008). In contrast, 13 healthy male volunteers exposed to either FA or dilute DE containing 300 µg/m³ PM for 1 h with 15-minute exercise/rest intervals found no increase in ET-1 levels over the next 24 h (Langrish et al., 2009). However, an increased sensitivity to ET-1 was found after the researchers went on to inject the volunteers with ET-1 peptide at 5 pmol/min. ET-1 infusion caused vasoconstriction after DE inhalation, but not after FA. Moreover, administration of 10 nmol/min of an ET_AR antagonist lessened the DE-induced vasoconstriction, confirming the involvement of ET-1 signaling. Therefore, although it should be noted that exposure studies involving vehicle exhaust do include air pollutants other than PM, the above reports suggest that PM exposure in humans increases the levels of, and sensitivity to, ET-1 peptide.

Animal inhalation models have provided insight into transcriptional changes of the *Et-1* gene, *Edn1*, following PM exposure in the lung, aorta, and heart. One study found an increase of *Edn1* transcription in the lung (Thomson et al., 2007), and another in the heart (Thomson et al., 2005; Ito et al., 2008; Kodavanti et al., 2011). In addition, two studies found that PM increased aortic *Edn1* expression (Campen et al., 2010; Kodavanti et al., 2011). Overall, PM exposure may upregulate *Edn1* transcription in the CV system.

While transcript expression level changes can be informative, the levels of circulating ET-1 peptide are a more relevant measurement as ET system activation, as decreased ET-1 removal can modify functionality without changing transcription status (Johnstrom et al., 2005). Studies in which experimental animals were exposed to PM consistently reported increases in circulating plasma ET-1 concentrations, regardless of the animal model or PM concentration used (Bouthillier et al., 1998; Thomson et al., 2005; Campen et al., 2006; Miyata et al., 2013). Increases in ET-1 concentrations become even more striking when considering that they are likely caused by short-term and tissue-specific ET-1 changes.

Additional supportive evidence has come from epidemiological and occupational studies. A single research group, Calderón-Garcidueñas and colleagues, authored three epidemiological studies of ET-1 levels in relation to ambient PM air pollution. All of these studies compared responses in children from two cities in Mexico (one urban and one rural) with differing ambient PM_{2.5} and O₃ levels, and found that increased PM_{2.5} exposure was associated with increased levels of circulating ET-1 (Calderon-Garcidueñas et al., 2007b, 2008, 2015).

An occupational study analyzed the association between the methylation status of *EDN1* and PM exposure (Tarantini et al., 2013). DNA methylation is an epigenetic mechanism by which gene expression can be regulated (Jaenisch & Bird, 2003). Though neither PM₁₀ nor PM₁ exposure was associated with *EDN1* methylation, both were associated with an increase in thrombin potential (Tarantini et al., 2013), an indicator of coagulation potential and thus a risk factor for disease (Siegemund et al., 2004). Increased thrombin potential was, in turn, associated with decreased *EDN1* DNA methylation (Tarantini et al., 2013). Interestingly, these researchers also found an association between zinc (Zn) exposure and *EDN1* hypomethylation. Zn is a common component of PM (Schwar et al., 1988; Tong & Lam, 1998; Harrison & Yin, 2000; Banerjee, 2003) and PM-associated Zn may mediate certain PM-induced cardiac effects (Kodavanti et al., 2002, 2008; Wallenborn et al., 2009).

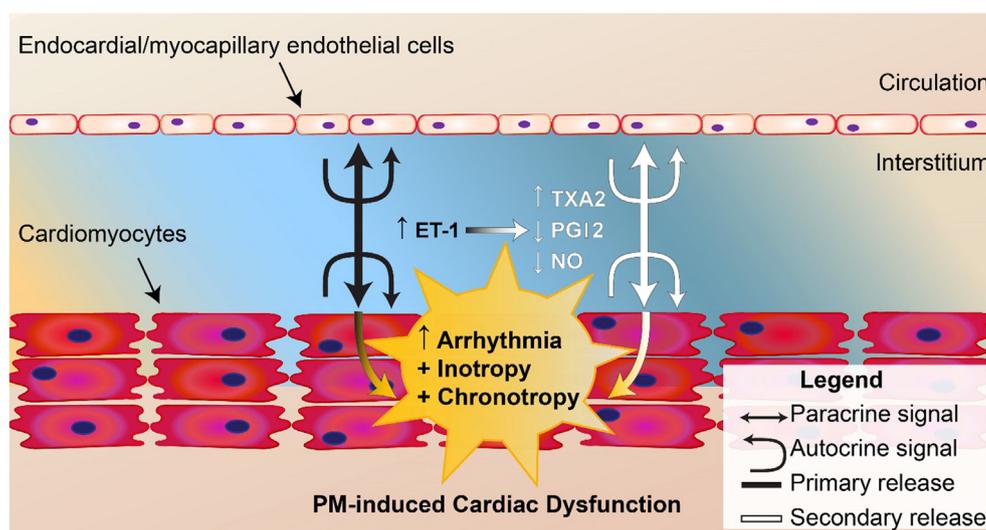


Fig. 1. Schematic drawing of potential ET-1 production and function in the heart following PM exposure. ET-1 is released by both endocardial/myocapillary endothelial cells and cardiomyocytes and functions as an autocrine/paracrine signaling agent. ET-1 signaling affects the release of secondary autocrine/paracrine factors, such as thromboxane A2 (TXA2), prostacyclin (PGI2), and NO. Changes in the concentrations of both primary and secondary autocrine/paracrine agents are likely important within the interstitium, though some changes can be observed in the circulation. Together, ET-1, increased TXA2, and reduced PGI2 and NO promote increased cardiac arrhythmias, positive cardiac inotropy, and positive cardiac chronotropy.

In addition, PM_{2.5} exposure upregulates ETR expression. Increased *Et_Ar* mRNA expression has been reported in the heart, aorta, and lung after rodent exposure to PM (Ito et al., 2008; Kodavanti et al., 2011; Upadhyay et al., 2014). This idea is further supported by an *in vitro* study in which arteries from rat cerebrum were cultured in an aqueous suspension of 1 µg/ml PM_{2.5}. PM_{2.5} exposure significantly increased *Et_Ar* and *Et_Br* mRNA and protein expressions, and enhanced receptor-mediated contractions (Xiao et al., 2015). While this concentration of PM_{2.5} is likely higher than would occur *in vivo*, this study demonstrates by proof-of-concept that direct tissue exposure to PM can increase ETR expression.

The few results finding no change or a decrease in ET-1 concentration after PM exposure could be due to several reasons, such as the type of PM air pollution, exposure length and concentration, and measurement timing. Nonetheless, when taken together, the human and animal studies strongly suggest that exposure to PM air pollution leads to systemic activation of the ET system. However, questions remain regarding ET effects on the heart.

4. Evidence of endothelin-1-mediated cardiac dysfunction following particulate matter exposure

Although the PM research community has begun to understand the vascular effects of ET-1 in CVD following PM exposure (Finch & Conklin, 2015), extravascular effects of ET-1 in this context have yet to be thoroughly investigated, particularly with regards to the direct effects of endothelins on cardiac tissue. Given that 1) PM exposure can increase ET-1 production, 2) PM exposure can result in cardiac dysfunction, and 3) ET-1 can function extravascularly to induce cardiac dysfunction, we propose that ET-1, as well as ET-1-induced secondary signaling agents, influence arrhythmia, MI, inotropy, and chronotropy in the heart following PM exposure (Fig. 1). Evidence integrating PM exposure, ET-1, and cardiac dysfunction into a single pathway is presented below.

A PubMed search was performed to identify publications that explored the role of ET-1 in mediating PM exposure-induced cardiac function¹. The limited body of literature that was identified and deemed

¹ The advanced PubMed search was performed on March 30, 2016 for “(particulate matter OR air pollution) AND (cardiac OR heart) AND (endothelin)”. Twenty-eight results were returned, one publication was added based on references from the returned articles, and 13 publications were deemed irrelevant and excluded. References are sorted by publication year.

relevant varied by type of model system, manner of ET-1 assessment (peptide vs. mRNA), cardiac endpoints considered, assessment timing, and exposure agent, concentration, and duration (Table 1). Eleven out of the 16 relevant publications described toxicological studies that used rats or mice as animal model systems, whereas the other five reported work with humans, and included two controlled human experiments, one epidemiological, and two occupational studies.

4.1. Epidemiologic evidence

The sole published epidemiological study investigating the relationships between PM_{2.5} exposure, ET-1, and cardiac function studied 28 healthy and non-smoking senior citizens (65 years of age or older) residing in nursing homes in Ontario, Canada (Liu et al., 2009). Daily personal, indoor, and outdoor PM_{2.5} concentrations were monitored, cardiac function was assessed in terms of HR, and circulating ET-1 peptide levels were ascertained. The median personal and indoor daily PM_{2.5} exposure levels across the three facilities were 6–7 µg/m³, and the daily median outdoor concentration was 15.3 µg/m³. Indoor PM_{2.5} concentration was associated with both circulating ET-1 peptide and HR, and personal and outdoor PM_{2.5} concentrations were each associated with HR, supporting the hypothesis that a relationship exists between PM_{2.5} exposure, ET-1, and HR.

4.2. Toxicological and controlled human exposure evidence

4.2.1. Exposure to particulate matter alone

Intratracheal instillation approaches have been used to better understand the relationships between PM-induced health effects and ET. Rodents exposed via intratracheal instillation to PM_{2.5} had increased ET-1 levels in the heart and decreased HR (Upadhyay et al., 2010). Instillation of 500 µg led to increased ET-1 three days later, and 1000 µg caused a similar increase within a single day. A second instillation exposure study subjected rats to a larger dose (2000 µg PM_{2.5}) and left coronary artery occlusion. The authors found worsened ventricular arrhythmia as compared to animals subjected to occlusion but not exposed to PM, in addition to elevated circulating ET-1 levels and decreased HR (Kang et al., 2002).

Manufactured particles with physiochemical properties similar to naturally occurring particles could provide additional mechanistic insight. The intratracheal instillation of multi-walled carbon nanotubes,

Table 1

Detailed information about studies assessing the relationship between ET-1 concentrations, cardiac function, and PM exposure listed chronologically.

Reference	Species	Exposure	PM-mediated changes in ET	PM-mediated changes in cardiac function
Haak et al., 1994	Humans (n = 10)	Low- and high-tar cigarettes	Increased circulating ET-1 levels within 10 min of smoking a high-tar cigarette	Increased HR after smoking a high-tar cigarette
Zhu et al., 1997	Rats (neonatal and adolescent)	Smoke from 96 cigarettes for 6 h per day for 5 days each week over 3 weeks, either in utero or as neonates	Increased circulating ET-1 levels after neonatal exposure	Increased infarct size after neonatal exposure
Vincent et al., 2001	Rats	Nose-only EHC-93 at 49 mg/m ³ for 4 h, with or without (EHC-93L) soluble components; 5 mg/m ³ diesel soot; 3 mg/m ³ carbon black	EHC-93 and EHC-93L increased circulating ET-1 at 32 and 2 h after exposure, respectively	No change in HR
Kang et al., 2002	Rats	Intratracheal instillation of 2 mg PM _{2.5} (Ying et al., 2014)	Increased circulating ET-1 peptide 2 h after installation; Increased ET _A R on cardiomyocytes in the infarct myocardium	Decreased HR, worsened arrhythmia, and premature ventricular contractions
Campen et al., 2006	Mice (ApoE ^{-/-})	Whole-body gasoline emissions at 60 µg/m ³ PM, with or without particles, during a 6 h per day exposure over 3 days	Increased circulating ET-1 levels with and without particulate-containing gasoline exhaust	T-wave deviation after exposure to gasoline exhaust containing particulates only; no change in HR
Scharrer et al., 2007	Humans (n = 20)	~3.5 mg/m ³ of steel welding fumes for 1 h and assessed 5 h later	Decreased circulating ET-1 levels	No change in HR or HRV
Ito et al., 2008	Rats	1–2 µg/m ³ PM _{2.5-1} CAPs for 4.5 h per day for 4 days per season, totaling 2–3.5 mg CAPs per season	Increased <i>Et_ar</i> and <i>Et-1</i> mRNA in the heart; No change of <i>Et-1</i> mRNA in the lungs	No change in HR
Upadhyay et al., 2008	Rats (WT and SHR)	172 µg/m ³ of PM _{0.1} for 24 h assessed 3 days later	Increased <i>Et-1</i> , <i>Et_ar</i> , and <i>Et_br</i> mRNA levels in the lungs, but not in the heart	Increased HR and decreased HRV
Brook et al., 2009	Humans (n = 31)	130 µg/m ³ PM _{2.5} CAPs + 109 ppb O ₃ from Toronto for 2 h on 3 occasions	Insignificant increase immediately after exposure; significant increase after FA exposure	Decreased HRV
Liu et al., 2009	Humans (n = 28)	Environmental exposure to PM _{2.5} and black carbon	Increased circulating ET-1 levels associated with indoor PM _{2.5}	Increased HR associated with personal, indoor, and outdoor PM _{2.5}
Upadhyay et al., 2010	Rats (WT and SHR)	Intratracheal instillation of 500 or 1000 µg PM _{2.5} CAPs	Increased ET-1 peptide in the heart; decreased ET-1 peptide in the lungs	Decreased HR after 1000 µg CAPs
Gentner & Weber, 2012	Rats	Secondhand cigarette smoke from 3 cigarettes over a 1 h exposure period every day for 28 days	No change in circulating ET-1 levels	Decreased HR
Jarvela et al., 2013	Humans (n = 20)	1.5–35 mg/m ³ (average 4 mg/m ³) of steel welding fumes for an 8 h work day	No change in circulating ET-1 levels	No change in HRV
Thompson et al., 2014	Rats	Intratracheal instillation of 10 or 100 µg multi-walled carbon nanotubes	Increased circulating ET-1 in the coronary effluent	Increased arrhythmia and infarct size
Upadhyay et al., 2014	Rats (Aged SHR)	~180 µg/m ³ of UF carbon particles for 24 h	ET-1 mRNA increased in the lungs and the heart; ETR mRNA increased in the lungs	Increased HR and decreased HRV
Zhang et al., 2015	Mice	Low (0.5 mg/m ³ SO ₂ , 0.2 mg/m ³ NO ₂) and high (3.5 mg/m ³ SO ₂ , 2 mg/m ³ NO ₂) exposures 6 h per day for 28 days with 1 or 10 mg/kg PM _{2.5} intranasal instillation every other day	ET-1 mRNA and peptide increased in cardiac tissue after high exposure	Increased HR after both exposures

CAPs, concentrated ambient particles; ET-1, endothelin-1; FA, filtered air; HR, heart rate; HRV, heart rate variability; NO₂, nitrogen dioxide; O₃, ozone; PM, particulate matter; SHR, spontaneously hypertensive; SO₂, sulfur dioxide; UF, ultrafine.

with or without ischemia/reperfusion injury, also altered the ET system and cardiac function (Thompson et al., 2014). Hearts isolated one day after whole-animal pulmonary instillation of 10 or 100 µg of multi-walled carbon nanotubes displayed an increased frequency of ventricular premature beats. In the same study, isolated hearts subjected to ex vivo ischemia and reperfusion displayed significantly increased ET-1 levels in the coronary effluent.

Inhalation studies of PM-mediated effects on ET-1 and cardiac dysfunction, likely more representative of human exposure, were first performed in rats. After a four hour exposure to high concentrations of EHC-93 (concentrated urban dust collected from Ottawa, Ontario; ~50 mg/m³) circulating ET-1 levels were increased (Vincent et al., 2001). Interestingly, EHC-93 particles that lacked the soluble components (as compared to total EHC-93) caused a more rapid increase in ET-1 levels, within 2 h post-exposure. However, there was no change in HR, the only measure of cardiac dysfunction collected in this study. A separate study found increased expression of *Et-1* and *Et_ar* mRNA in the hearts of rats that inhaled much lower concentrations (1–2 µg/m³) of concentrated ambient particles (CAPs; unaltered particles 0.1 to 2.5 µm

in diameter collected from the ambient air) 4.5 h per day for four days, also without a parallel change in HR (Ito et al., 2008).

Two papers by the same group evaluated the effects of inhaling ~175 µg/m³ ultrafine (UF) carbon particles on HR and HRV in spontaneously hypertensive rats. In the first study, the authors demonstrated that inhalation of UF carbon particles caused an increase in HR and a decrease in HRV after exposure, which temporally correlated with significant induction of *Et-1* and *Et_ar* mRNA in the lung (Upadhyay et al., 2008). Increases in *Et-1* mRNA were observed in the heart, but did not reach statistical significance. The second study by that group performed a similar experiment, but this time with aged (12–13 months) spontaneously hypertensive rats. Inhalation of UF carbon particles led to significantly increased HR, decreased HRV, and increased *Et-1* and *Et_ar* mRNA levels in the heart and lungs after exposure (Upadhyay et al., 2014).

4.2.2. Exposure to particulate matter as a component of a mixture

Real-world ambient air pollution is a complex mixture that typically includes PM, gases, volatile and semivolatile compounds, and other pollutants. Although exposure to mixtures makes interpreting PM-specific

effects more difficult, it can provide insight into the effects of PM in mixtures such as welding fumes, cigarette smoke (CS), and vehicle exhaust.

A study of PM_{2.5}, SO₂, and NO₂ co-exposure also supported a role for PM in ET production and cardiac effects (Zhang et al., 2015). Mice were exposed to two co-exposure doses for 28 days. The low dose was comprised of intranasal instillation of 1 mg/kg every other day alongside exposure to 0.5 mg/m³ SO₂ and 0.2 mg/m³ NO₂ for 6 h per day, while and the high dose followed a similar schedule but increased the instillation amount to 10 mg/kg and the SO₂ and NO₂ concentrations to 3.5 and 2 mg/m³, respectively. Both co-exposure dose resulted in increased HR, and the high dose also resulted in increased levels of ET-1 peptide and mRNA in the cardiac tissue.

Two occupational studies of welding fume exposure looked at effects of relatively high concentrations (3.5 and 4 mg/m³) over short timeframes (1 and 8 h, respectively) (Scharer et al., 2007; Jarvela et al., 2013). Volunteers exposed for 1 h displayed a very small (0.3 pg/mL), but statistically significant, decrease in circulating ET-1 levels and no changes in HR or HRV metrics 5 h later (Scharer et al., 2007). Steel welders evaluated before and after working a typical eight-hour day preceded by a two-day work break exhibited no change in circulating ET-1 or HRV (Jarvela et al., 2013). Since subjects had been working as welders for an average of >13 years, it is possible that that they became acclimated to the conditions and no longer experienced an activation of the ET system in response to welding fumes.

Exposure to CS caused alterations in the ET and cardiac related endpoints in three reports. In a controlled human exposure study performed >20 years ago, an increase in circulating ET-1 was found within 10 min of smoking with a corresponding increase in HR (Haak et al., 1994). Not long after, it was reported that neonatal rats exposed to high concentrations of CS (1440 cigarettes over a 3 week period) displayed increased circulating ET-1 peptide levels (Zhu et al., 1997). After subjecting the rodents to left coronary artery occlusion and reperfusion, the CS-exposed group also exhibited increased infarct size, an indicator of cardiac dysfunction, as compared to the unexposed group. More recently, rats exposed to 84 cigarettes over a 28 day period showed no change in circulating ET-1 peptide levels, though HR did decrease (Gentner & Weber, 2012).

Inhalation of gasoline and DE mixtures containing PM may also lead to changes in cardiac rhythm. One study showed rhythmicity changes and ET-1 peptide level increases at PM exposure concentrations as low as 60 µg/m³ (Campen et al., 2006). A particularly intriguing publication assessed CV function after simultaneous exposure of PM_{2.5} and O₃ to humans (Brook et al., 2009). Though the authors found that an ET-1 antagonist abrogated exposure-induced BP elevations, the ability to

attribute effects specifically to PM was limited, as effects of exposure to PM_{2.5} alone were not assessed.

The above research points to a potential role of ET-1 signaling in PM-mediated cardiac dysfunction. Specific evidence for and against ET-1 involvement in HR, HRV, arrhythmia, and MI is presented in Table 2, which summarizes the results of the studies in Table 1 by cardiac endpoint. Although Table 2 provides a different perspective on the current body of literature listed in Table 1, it does not examine the reasons why certain investigations reported different results, which could arise from differences in PM type, concentration, and exposure duration. In addition, most studies did not specifically evaluate ET-1 levels within the heart, making it difficult to interpret cardiac-specific ET-1 changes after PM exposure.

5. Endothelin-1 and the release of secondary cardiac-active mediators

ET-1 can promote the production and release of additional autocrine/paracrine signaling agents in the heart, which can exacerbate or antagonize ETR-mediated signaling effects (Jenkins et al., 2009; Noireaud & Andriantsitohaina, 2014). These agents include NO and prostaglandins such as prostacyclin (PGI₂) and thromboxane A₂ (TXA₂). PGI₂ is commonly regarded as a vasodilator and an inhibitor of clot formation, whereas TXA₂ is a vasoconstrictor with prothrombotic activity (Kawabe et al., 2010).

5.1. Cardiac-specific effects of nitric oxide

NO release is a downstream effect of ET_BR signaling (Verhaar et al., 1998). NO is generally regarded as a positive lusitropic agent, increasing myocardial relaxation during diastole (Rastaldo et al., 2007). NO effects on cardiac inotropy (the force of contraction) have been more puzzling. NO may increase inotropy via the nitrosylation of various cardiac proteins involved in excitation-contraction coupling and stretch-induced contractility (Noireaud & Andriantsitohaina, 2014). However, negative inotropic effects have been reported at higher NO concentrations (Brutsaert, 2003).

5.2. Cardiac-specific effects of prostaglandins

Prostaglandins are involved in various functions in the myocardium, including alterations in gene transcription, ion channel kinetics, and hemodynamics (Jenkins et al., 2009). Although prostaglandins can preserve normal heart function during physiological challenges, chronic or

Table 2
Evidence for ET-1 involvement in cardiac dysfunction following PM exposure.

Heart rate (11 studies)	↑ HR (4 studies)	↑ ET-1 (3 studies)	Haak et al., 1994 [‡] Liu et al., 2009 [‡] Upadhyay et al., 2014 [†] Upadhyay et al., 2008 [†] Kang et al., 2002 [†] Upadhyay et al., 2010 [†] Zhang et al., 2015 [†]
	↓ HR (4 studies)	NC in ET-1 (1 study) ↑ ET-1 (3 studies)	Gentner & Weber, 2012 [†] Vincent et al., 2001 [†] Ito et al., 2008 [†] Scharer et al., 2007 [‡] Upadhyay et al., 2014 [†] Upadhyay et al., 2008 [†]
	NC in HR (3 studies)	NC in ET-1 (1 study) ↑ ET-1 (2 studies)	Brook et al., 2009 [‡] Jarvela et al., 2013 [‡] Scharer et al., 2007 [‡] Kang et al., 2002 [†] Campen et al., 2006 [†] Thompson et al., 2014 [†] Zhu et al., 1997 [†] Thompson et al., 2014 [†]
Heart rate variability (5 studies)	↑ HRV (3 studies)	↓ ET-1 (1 study) ↑ ET-1 (1 study) NC in ET-1 (2 studies)	
	NC in HRV (2 studies)	NC in ET-1 (1 study) ↓ ET-1 (1 study) ↑ ET-1 (3 studies)	
Arrhythmia (3 studies)	↑ arrhythmia (3 studies)		
Myocardial infarction (2 studies)	↑ infarct size (2 studies)	↑ ET-1 (2 studies)	

[†], Animal subjects; [‡], human subjects; NC, no change; ↑, increase; ↓, decrease; HR, heart rate; HRV, heart rate variability.

persistent prostaglandin release in the heart can adversely affect the conversion of an action potential to a contraction in a muscle fiber, known as excitation-contraction coupling (Neef & Maier, 2013), possibly leading to HF, arrhythmia, or even sudden cardiac death.

The first evidence that ET-1 caused prostaglandin release was published in 1988 (de Nucci et al., 1988). The perfusate of isolated lungs of guinea pigs and rats infused with ET contained the prostaglandins PGI₂ and TXA₂. In addition, PGI₂ was released when isolated rabbit hearts were perfused with ET-1 (Karwatowska-Prokopczuk & Wennmalm, 1990). ET-1 stimulation of rat vascular smooth muscle cells also increased thromboxane B₂ (a more stable and easily measurable metabolite of TXA₂ formed rapidly in the circulation) levels in cell culture media (Takayasu-Okishio et al., 1990). In addition, intravenous injection of ET-1 in guinea pigs caused an increase in MAP, bronchoconstriction, and thromboxane B₂ levels in bronchoalveolar lavage fluid (Lueddeckens et al., 1993). All of these changes were reduced or abrogated by eliminating the effects of TXA₂, while maintaining ET-1 signaling, demonstrating the specific effects of ET-1 mediated TXA₂ release. Prostaglandin synthesis is now a generally accepted downstream effect of ET-1 signaling.

Similar to the relationship between NO and ET-1, the effects of the prostaglandins PGI₂ and TXA₂ are generally thought to counterbalance each other, and when the regulation of either is altered, adverse health effects can occur. Interestingly, TXA₂ and PGI₂ concentrations in the local myocardium have been shown to correlate with early post-ischemic arrhythmias in canines (Coker et al., 1981). In this report, subjects with elevated arrhythmia counts had elevated TXA₂ and reduced PGI₂ levels, whereas subjects with low arrhythmia counts had low TXA₂ and elevated PGI₂. Because of this, secondary autocrine/paracrine signaling responses during CV injury are thought to exacerbate the pro-arrhythmogenic effects of ET-1. This is exemplified during cardiac ischemia/reperfusion, a state in which ET-1 release from the heart increases (Brunner et al., 1992). If ET-1 initiates TXA₂ release in cardiac tissue, the effects of ET-1 during adverse events like cardiac ischemia/reperfusion would be exacerbated.

5.3. Secondary release of prostaglandin and nitric oxide in the context of endothelin-1 and particulate matter exposure

Several lines of research have shown that PM exposure leads to cyclooxygenase (COX) activation and prostaglandin synthesis (Calderon-Garciduenas et al., 2007a; Maier et al., 2008), possibly due to ET-1 signaling, but the connection between ET-1 and secondary prostaglandin release is not yet clear. However, experiments employing COX inhibitors have demonstrated that prostaglandins mediate coronary vascular effects of ET-1 following pulmonary exposure to engineered nanomaterials. For example, pulmonary exposure to multi-walled carbon nanotubes in rats lead to increased release of cardiac ET-1 and depression of coronary flow during early reperfusion in isolated hearts subjected to ischemia/reperfusion one day after exposure, ultimately resulting in the expansion of MI (Thompson et al., 2014). Moreover, this study showed that coronary artery segments isolated from rats one day post-instillation generated increased force during ET-1 vasoconstrictions. The increased force was attenuated with COX inhibition, TXA₂ synthetase inhibition, and TXA₂ receptor antagonism, showing the functional effect was downstream of ET-1 signaling. Similarly, pulmonary instillation of carbon fullerenes caused rat coronary arteries isolated 24 h after exposure to respond with increased force generation during ET-1 vasoconstriction, which was attenuated with COX inhibition (Thompson et al., 2014). Although secondary ET-1 responses, likely mediated by TXA₂, were not associated with ambient PM, it seems plausible that PM exposure from ambient air pollution sources could cause similar responses.

In summation, there is a large body of evidence demonstrating that ET-1 induces the release of secondary autocrine/paracrine mediators. As many of these secondary mediators can also influence cardiac

function, they should be considered when investigating downstream effects of ET-1.

6. Endothelin receptor-targeted therapeutics and particulate matter

6.1. Endothelin receptor-targeted therapeutics

Understanding of the ET system quickly led to the development of ways in which the system could be manipulated. ET-1 antagonists were developed (Ihara et al., 1991; Spinella et al., 1991; Atkinson & Pelton, 1992; Bazil et al., 1992; Fukuroda et al., 1992; Ihara et al., 1992; Breu et al., 1993; Clozel et al., 1993, 1994) almost immediately after the two mammalian ETRs were identified (Arai et al., 1990; Sakurai et al., 1990). Certain ET_AR antagonists can reverse established ET-1-mediated constriction (Pierre & Davenport, 1999), suggesting that ET_AR antagonists can displace ET-1 or induce receptor internalization and degradation.

Unsurprisingly, it was thought that ETR antagonists could be employed as therapeutics for various ET-related health effects, and multiple clinical trials tested this hypothesis. Trials for pulmonary arterial hypertension (PAH) and scleroderma-related digital ulcers were promising, however several other trials found no difference in, or even a worsening of, health outcomes after treatment with ETR antagonists (Kohan et al., 2012). After extensive analysis of potential causes, it was concluded that poor study design and patient selection, combined with mechanistically-predictable side effects, likely skewed the results.

Foreseeable side effects of ETRs, mainly due to downstream ET_BR signaling, have caused several trials to be terminated prior to completion. The most problematic side effect has been fluid retention, which is associated with the use of virtually all known ETR antagonists (Battistini et al., 2006). Fluid retention has negatively impacted several clinical trials, such as one testing avosentan. Although avosentan treatment appeared to improve kidney function, it also caused a large increase in the number of patients with severe fluid retention and CHF, as compared to the patients receiving a placebo (Mann et al., 2010). This is not surprising as ET_BR signaling in the kidneys can regulate renal sodium and water transport (Kohan, 2006), allowing for the simultaneous improvement of kidney function and increase of fluid retention. A separate human trial that was performed during the above mentioned trial showed that fluid retention due to avosentan was dosage-dependent, and that avosentan could improve overt diabetic nephropathy at lower dosages than were being used (Wenzel et al., 2009), underscoring the importance of dosage when designing informative clinical trials.

Functional events initiated by the two ETRs differ, suggesting that selectively antagonizing ET_AR to reduce pathophysiological effects while maintaining ET removal by ET_BR would be optimal. However, the first ETR antagonist to be approved for human treatment in the US and Europe was the dual receptor antagonist bosentan (Rubin & Roux, 2002). Five years later ambrisentan, a somewhat ET_AR-selective antagonist, entered the market. Ambrisentan was soon followed by sitaxsentan, a highly ET_AR-selective antagonist (Maguire & Davenport, 2014). In 2010, four patients receiving sitaxsentan died of liver failure and five others experienced severe hepatitis-like drug reactions, spurring its withdrawal from the market and the termination of ongoing trials (Galie et al., 2011). Though the number affected was small, no deaths related to liver toxicity had been reported in the >90,000 patients treated with bosentan or ambrisentan. Though liver toxicity is unlikely related to receptor isoform specificity, these unfortunate occurrences further reduced interest in pursuing ETR antagonists as clinical therapeutics.

Poor study design may have also contributed to the failure of effective and relatively safe ETR antagonist therapeutics. A Phase III study of the relatively-selective ET_AR antagonist darusentan in patients with resistant hypertension found a significant reduction in ambulatory BP (Bakris et al., 2010). However the trial was halted after finding no effect

in the primary endpoint, sitting BP. Now, due to the selection of a suboptimal health endpoint, research involving a drug demonstrated to be effective at reducing ambulatory BP in persons where other drugs have failed is unlikely to receive additional trials required for FDA approval.

Nevertheless, a recently developed ETR antagonist may have provided a reason to continue researching these types of therapeutics. Modifications to the nonselective receptor antagonist bosentan that decreased adverse side effects, increased tolerability, and improved efficacy led to the development of macitentan (Bolli et al., 2012). Macitentan was approved by the FDA in 2013, and has since been generally accepted as the preeminent available ETR antagonist. This is due to several reasons, such as reductions in fluid retention, liver toxicity, and interactions with other drugs as compared to bosentan. In addition, macitentan is functional for a longer period of time after administration than bosentan. This increase has been credited to both the generation of a long-lasting and pharmacologically active (~48 h) metabolite of macitentan and that macitentan remains bound to ETRs for longer than bosentan, possibly due to binding site differences (Iglarz et al., 2008; Sidharta et al., 2011; Sidharta et al., 2013). Importantly, although macitentan was based on bosentan, it does display selectivity for ET_AR (Iglarz et al., 2008). These advantages position macitentan as both a useful PAH treatment option and a potential therapeutic for other ET-related pathologies.

6.2. Endothelin receptor antagonists and particulate matter

With the wide selection of ETR antagonists available and the involvement of ET production after PM exposure, it is surprising that so few studies have used ETR antagonists in the investigation of PM. Only 14 studies utilized ETR antagonism to better understand mechanisms following PM exposure² (Table 3). The majority of these studies used CS or CS extract as the exposure agent and evaluated very specific mechanistic endpoints, such as arterial contraction and changes in ET_BR expression levels (Dadmanesh & Wright, 1997; Wright et al., 1999; Rahman et al., 2007; T.M. Bhavsar et al., 2008; T. Bhavsar et al., 2008; Chen et al., 2010; Milara et al., 2010, 2012; Huang et al., 2013; Aslani et al., 2015). ET-1 was demonstrated to mediate several effects of CS exposure, such as ET_BR expression and vessel constriction. However, no studies utilizing ETR antagonists have investigated the direct effect of ET-1 on PM-induced cardiac events, or looked at PM-related cardiac events in people already taking them for PAH or scleroderma-related digital ulcers.

Four studies using ETR antagonists have provided insight into the mechanisms of PM-mediated CVD. One exposed proatherosclerotic mice to gasoline engine exhaust containing 60 µg/m³ PM 6 h a day for seven days, while also administering the ET_AR-specific antagonist BQ123 (Lund et al., 2009). The antagonist abrogated PM-exposure mediated increases in aortic *Et-1* mRNA, as well as transcription of matrix metalloproteinase 9 (Lin et al., 2014), suggesting a role for ETR signaling in the progression of atherosclerosis. In a DE exposure study, ET_BR were reported to mediate the vasoconstriction of intraseptal coronary arteries after rats were exposed to 300 µg/m³ PM for 5 h (Cherng et al., 2009). The two remaining studies involved human subjects. One found that ETR mediated changes in forearm blood flow after 1 h of exposure to dilute DE at 300 µg/m³ PM (Langrish et al., 2009). The other human study concurrently exposed human volunteers to ~130 µg/m³ ambient PM_{2.5} and 120 ppb O₃ three times, each for a duration of 2 h (Brook et al., 2009). Pretreatment with a 250 mg dose of bosentan, a nonselective ETR antagonist, decreased BP and increased HR in response

Table 3
Evidence that ETR antagonism alters PM effects.

Exposure	ETR-mediated functional effect	Reference
CAPs	Diastolic BP	Brook et al., 2009‡
Cigarette smoke	Cell proliferation in the airways and arterial vasculature of the lung	Dadmanesh & Wright, 1997†
	ET _B R expression	Huang et al., 2013†
	Aortic and carotid artery contraction	Rahman et al., 2007†
	ETR expression	Milara et al., 2012‡
	Lung inflammation	T.M. Bhavsar et al., 2008†
	Neutrophil recruitment to the lungs	T. Bhavsar et al., 2008†
	Spermatogonia and spermatocyte number	Aslani et al., 2015†
Cigarette smoke extract	Airway resistance	Wright et al., 1999†
	ET _B R expression	Milara et al., 2010‡
	Apoptosis and inflammatory cytokine production	Chen et al., 2010†
Diesel exhaust	ET _A R-mediated vasoconstriction	Langrish et al., 2009‡
	ET _B R-mediated arterial constriction	Cherng et al., 2009†
Gasoline exhaust	MMP-9, MMP-2, ROS, and ET-1 expression in the vasculature	Lund et al., 2009†

†, Animal model; ‡, human model; BP, blood pressure; CAPs, concentrated ambient particles; CS, cigarette smoke; DE, diesel exhaust; ET-1, endothelin-1; ET_BR, endothelin B receptor; ETR, endothelin receptor; HR, heart rate; MMP, matrix metalloproteinase; ROS, reactive oxygen species.

to PM_{2.5} and O₃. As such, ETRs appear to be involved in the ET-1 vascular response to PM. However, thus far pharmacological intervention studies targeting ET-1-mediated extravascular cardiac effects of PM exposure are lacking.

Regarding the studies in this section, it should be noted that pharmacological interventions, while valuable, are limited in their implications. For example, when administering ETR antagonists *in vivo*, the vascular and extravascular effects of ET-1, as well as effects on organ systems other than the heart, are difficult to tease apart. Although studies that incorporate the use of organ-specific ETR-deficient models may be more definitive in establishing the role of ET-1 in air pollution-induced cardiac health effects, the above intervention studies do suggest that ETR antagonists may reduce negative effects on the cardiovascular system after exposure to PM.

7. Conclusions and remaining questions

The individual bodies of literature regarding PM and ET are each vast, but the two fields have yet to be sufficiently integrated. In general terms, exposure to certain types of PM can lead to upregulation of ET-1 in various tissues (Finch & Conklin, 2015), and both ET-1 signaling and PM exposure can cause and exacerbate CVD (Franklin et al., 2015). Very few studies have attempted to tie these findings together, and the majority of those that have focused on the vascular effects of ET-1, such as vessel constriction (Finch & Conklin, 2015). Though vascular effects of ET may be less complicated to observe and measure, effects of ET outside of the vasculature, such as direct cardiac effects, should not be overlooked. It will also be important to examine how ischemia resulting from ET-induced vasoconstriction of coronary vessels might exacerbate cardiac-specific effects such as inotropy, chronotropy, and arrhythmia, and vice versa. In other words, increased inotropy and chronotropy could further exacerbate ischemic injury in the heart by increasing blood demand when supply is reduced. Additional work using lessons learned from all relevant lines of research could be informative, potentially paving the path toward an improved understanding of PM-induced cardiac dysfunction. As such, several important unanswered research questions remain, a few of which we discuss below.

The mechanism by which PM exposure leads to ET upregulation within the heart has yet to be fully elucidated. As increases in ET-1

² An advanced PubMed search was performed on March 30, 2016 for "(particulate matter OR air pollution) AND (endothelin receptor antagonist OR bosentan OR ambrisentan OR avosentan OR darusentan OR macitentan OR sitaxsentan)". Fourteen results were returned, four of which were excluded for relevance. Four studies were added based on references from the returned articles and prior knowledge.

have been observed in the absence of pulmonary and systemic inflammation (Campen et al., 2005, 2006; Upadhyay et al., 2008; Liu et al., 2009), mechanisms other than inflammation are likely to be involved in the activation of the ET system after PM exposure. Direct particle translocation could account for the rapid timing of effects observed after exposure, however only a small amount of PM is likely able to leave the lungs (Brown et al., 2002; Burch, 2002; Mills et al., 2005; Wiebert et al., 2006a, 2006b; Moller et al., 2008; US EPA, 2009) and access the heart. Initiation via an autonomic pathway remains a plausible explanation, although evidence in support of this proposed mechanism is limited. Interestingly, PM exposure has been shown to increase norepinephrine concentrations in the lung (Chiarella et al., 2014), brain (Sirivelu et al., 2006) and urine (Ying et al., 2014). Independently, norepinephrine infusion can upregulate ET-1 expression in the heart (Kaddoura et al., 1996). These separate lines of research suggest that PM exposure may activate an autonomic pathway leading to ET-1 production in the heart. This autonomic pathway could then be exacerbated by extravascular effects of ET-1. Once expression has increased in the heart, ET-1 can activate cardiac sympathetic afferent nerves and trigger a positive-feedback, sympathoexcitatory reflex (Fu et al., 2010). In addition, ET-1 production in the brain following PM exposure (Ohno et al., 2004; Thomson et al., 2007; Guo et al., 2012) can enhance the cardiac sympathetic afferent reflex (Chen et al., 2012b). In a similar vein, ET-1 produced in the lungs following PM exposure (Upadhyay et al., 2008, 2014) could sensitize and/or activate airway sensory afferent nerves, as was demonstrated in peripheral C-fibers (Namer et al., 2008). As such, ET-1 upregulation in the heart following PM exposure could be mediated by norepinephrine release and enhanced by ET-1-mediated nerve activation in the lungs, heart, and brain.

ET produced by cardiac tissue after PM exposure could differ in timing or magnitude from changes in circulating or lung ET-1. Of the five studies that looked at ET-1 peptide or mRNA changes specifically within the heart after PM exposure, three studies only measured changes in *Edn1* mRNA levels, one only assessed ET-1 peptide levels, and one paper evaluated both. Three reports found increased *Edn1* mRNA levels (Ito et al., 1993; Upadhyay et al., 2010), whereas one found no change (Upadhyay et al., 2008). However, as increased transcription may not reflect the rate of biologically active ET-1 peptide synthesis or account for peptide sequestration efficiency, changes in transcription may not reflect local ET-1 peptide level changes within heart tissue. The two studies that directly evaluated ET-1 peptide levels in the heart both found significant increases (Upadhyay et al., 2010; Zhang et al., 2015), providing sufficient rationale for additional studies to confirm this finding. Cardiac tissue from model systems could be used to provide further evidence of PM-mediated increases in ET-1 peptide levels, as well as to determine which cell types produce or are affected by ET-1 (e.g., cardiomyocytes vs. endocardial/myocardial endothelial cells). If PM increases ET-1 peptide levels in exposed animals, it would be useful to also confirm this finding in humans. Outside of obtaining excess material from myocardial biopsies in humans, research may be limited to animal studies and human in vitro studies in order to correlate cardiac ET-1 changes with PM exposure and adverse cardiac events in humans, which could still potentially provide convincing evidence that PM leads to ET production in the heart.

While confirming that ET-1 peptide production in the heart is increased after PM exposure would strongly suggest that ET-1 may mediate cardiac dysfunction in this context, mechanistic studies are needed to verify this hypothesis and more clearly describe the types of cardiac dysfunction resulting from PM exposure. This is possible, as an array of ETR antagonists and agonists with varying receptor specificities are available to confirm that ET contributes to PM-induced CVD. Use of ETR agonists and antagonists in animal models to attenuate and exacerbate, respectively, adverse CV effects after PM exposure could provide clear mechanistic evidence of the involvement of ET. Isolated perfused heart preparations could be utilized to extricate extravascular from vascular ET effects on cardiac function. Alternatively, retrospective human

epidemiological studies comparing CV outcomes in patients that have or have not taken ETR therapeutics could present additional insight on the role of ET-1 signaling in humans.

Additional research is needed to better understand the impact of ET-mediated secondary release of autocrine/paracrine agents on the development and progression of CVD following PM exposure, specifically within the heart. Physiologically, endocardial/myocardial endothelial cells are co-located so that ET may preferentially influence cardiomyocyte function (Fig. 1). Because of this, it would be interesting to further tease apart direct ET-1 effects from those of the numerous secondary autocrine/paracrine agents within the heart after various PM exposure scenarios, possibly using cell co-culture systems. In turn, characterizing the cardiac-specific effects of secondary ET-1 signaling from the vascular-specific effects within the heart could provide an initial mechanistic understanding of the cascade of events following ET-1 upregulation.

Here we have proposed and supported the idea that altered autocrine/paracrine signaling directly influences cardiac function and can lead to certain cardiac health effects of PM exposure. ET-1 was selected as a case study for this hypothesis, as it may be a central mediator involved in the propagation of CV health consequences initiated by pulmonary exposure to PM. Alterations in other autocrine/paracrine signaling agents, such as TXA₂, PGI₂, and NO, also are logical candidates, but are each linked to ET-1. Given the population-wide impacts of PM, improving insight into how ET signaling in the heart can be influenced by PM exposure would likely positively impact treatment approaches for CV disease.

Funding sources

This research was supported in part by appointments to the Research Participation Program for the U.S. EPA, Office of Research and Development, administered by Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and EPA.

Contributions

E. A. W. Chan and L. C. Thompson developed the idea for the manuscript and E. A. W. Chan wrote the first draft. B. Buckley, A. K. Farraj, and L.C. Thompson performed extensive revisions, and all authors have approved the final manuscript.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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Acknowledgments

We thank Dr. Erin Hines, Dr. Urmila Kodavanti, Dr. Kristen Rappazzo, Dr. James Brown, Dr. Steven Dutton, and Dr. John Vandenberg for helpful comments on the manuscript and Molly Windsor for assistance with the figure.

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