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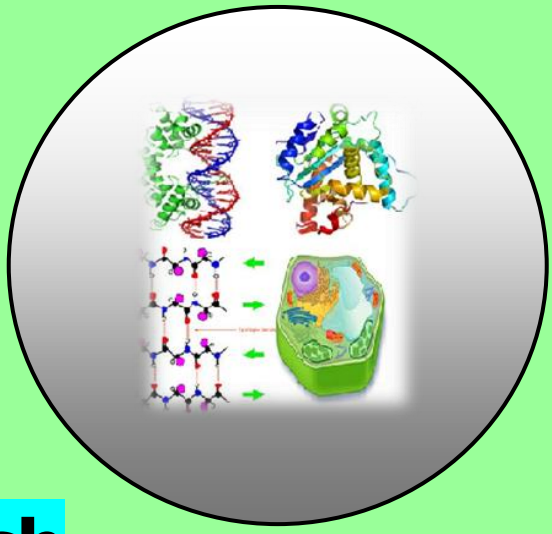

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REVIEW ARTICLE

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Erythropoietin in Hypertension: A Review

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ABSTRACT

Hypertension is a public health disease whic is increasing at an alarming rate.It occurs mostly in the elderly but theses days can occur at any age bracket.It is a major health concern both to the developing and developed contries in the World. Hypertension is a chronic medical condition in which the blood pressure in the arteries is elevated. Normal blood pressure at rest is within the range of 100–140 mmHg systolic and 60–90 mmHg diastolic. Hypertension is present if the blood pressure is persistently at or above 140/90 (mmHg).Hypertension mostly affect the kidneys of the patients which affect synthesis and release of erythropoietin and will affect both the erythropoiesis leading to anaemia and other non-erythropoietic functions of erythropoietin.The paper is a review on erythropoietin in hypertension.
Keywords: Erythropoietin, Hypertension, Anaemia and Kidney.

INTRODUCTION

Hypertension is a chronic medical condition in which the blood pressure in the arteries is elevated. Blood pressure is expressed by two measurements, the systolic and diastolic pressures, which are the maximum and minimum pressures, respectively, in the arterial system. The systolic pressure occurs when the left ventricle is most contracted; the diastolic pressure occurs when the left ventricle is most relaxed prior to the next contraction. Normal blood

pressure at rest is within the range of 100–140 mmHg systolic and 60–90 mmHg diastolic. Hypertension is present if the blood pressure is persistently at or above 140/90 millimeters mercury (mmHg) for most adults; different criteria apply to children (James *et al.,*2013).

Dietary and lifestyle changes can improve blood pressure control and decrease the risk of health complications, although treatment with medication is still often necessary in people for whom lifestyle changes are not enough or not effective. The treatment of moderately high arterial blood pressure (defined as >160/100 mmHg) with medications is associated with an improved life expectancy (Diao *et al.,* 2012; Arguedas *et al.*, 2013). Erythropoietin (EPO) is a glycoprotein hormone that controls erythropoiesis, or red blood cell production. It is a cytokine for erythrocyte precursors in the bone marrow. Human EPO has a molecular weight of 34 kDa.It is produced by interstitial fibroblasts in the kidney in close association with peritubular capillary and tubular epithelial tubule. It is also produced in perisinusoidal cells in the liver. While liver production predominates in the fetal and perinatal period, renal production is predominant during adulthood. In addition to erythropoiesis, erythropoietin also has other known biological functions. For example, it plays an important role in the brain's response to neuronal injury (Siren *et al.,*2001). EPO is also involved in the wound healing process (Haroon *et al.,* 2003). Uremia affects the lung with pathological alterations that worsen, as the disease progresses.Particularly noteworthy are anomalies in the transport of respiratory gases, alterations in diffusive mechanisms, diminution in ventilatory processes at rest, and functional alterations in the respiratory muscles. These patients, moreover, almost always present a significantly higher cardiac ejection fraction, low hemoglobin and hematocrit levels, and an increase in the pulmonary arteria lpressure (PAP). The PAP usually tends to normalize, whenever arteriovenous fistula closure is undertaken, e.g., when the patient undergoes renal transplantation (Drueke *et al*., 2006). Chronic hypoxia elicits a number of physiological responses that result in PH. Hypoxia causes active pulmonary vasoconstriction as well as a structural remodeling of the pulmonary arterial vasculature. Both of these responses diminish the luminal diameter of the small pulmonary arteries, increasing vascular resistance and contributing to the development of PH .

Hypertension

Hypertension also known as high blood pressure or arterial hypertension, is a chronic medical condition in which the blood pressure in the arteries is elevated. Blood pressure is expressed by two measurements, the systolic and diastolic pressures, which are the maximum and minimum pressures, respectively, in the arterial system. The systolic pressure occurs when the left ventricle is most contracted; the diastolic pressure occurs when the left ventricle is most relaxed prior to the next contraction. Normal blood pressure at rest is within the range of 100–140 mmHg systolic and 60–90 mmHg diastolic. Hypertension is present if the blood pressure is persistently at or above 140/90 millimeters mercury (mmHg) for most adults; different criteria apply to children (James *et al.,* 2013).

Hypertension usually does not cause symptoms initially, but sustained hypertension over time is a major risk factor for hypertensive heart disease, coronary artery disease(Lewington *et al.*,2002), stroke, aortic aneurysm, peripheral artery disease, and chronic kidney disease.

Hypertension is classified as either primary (essential) hypertension or secondary hypertension. About 90–95% of cases are categorized as primary hypertension, defined as high blood pressure with no obvious underlying cause (Carretero *et al.,* 2000). The remaining 5–10% of cases are categorized as secondary hypertension, defined as hypertension due to an identifiable cause, such as chronic kidney disease, narrowing of the aorta or kidney arteries, or an endocrine disorder such as excess aldosterone, cortisol, or catecholamines.

Dietary and lifestyle changes can improve blood pressure control and decrease the risk of health complications, although treatment with medication is still often necessary in people for whom lifestyle changes are not enough or not effective. The treatment of moderately high arterial blood pressure (defined as >160/100 mmHg) with medications is associated with an improved life expectancy (Diao *et al.,* 2012; Arguedas *et al.*, 2013). The benefits of treatment of blood pressure that is between 140/90 mmHg and 160/100 mmHg are less clear, with some reviews finding no benefit and other reviews finding benefit (Sundstrom *et al.*, 2015).

Signs and symptoms

Hypertension is rarely accompanied by any symptoms, and its identification is usually through screening, or when seeking healthcare for an unrelated problem. Some with high blood pressure report headaches (particularly at the back of the head and in the morning), as well as lightheadedness, vertigo, tinnitus (buzzing or hissing in the ears), altered vision or fainting episodes. These symptoms, however, might be related to associated anxiety rather than the high blood pressure itself.

On physical examination, hypertension may be associated with the presence of changes in the optic fundus seen by ophthalmoscopy (Wong *et al.,* 2007). The severity of the changes typical of hypertensive retinopathy is graded from I–IV; grades I and II may be difficult to differentiate. The severity of the retinopathy correlates roughly with the duration and/or the severity of the hypertension (Fisher and Williams, 2015).

Secondary hypertension

Hypertension with certain specific additional signs and symptoms may suggest secondary hypertension, i.e. hypertension due to an identifiable cause. For example, Cushing's syndrome frequently causes truncal obesity, glucose intolerance, moon face, a hump of fat behind the neck/shoulder, and purple abdominal stretch marks (Marik *et al.,* 2007). Hyperthyroidism frequently causes weight loss with increased appetite, fast heart rate, bulging eyes, and tremor. Renal artery stenosis (RAS) may be associated with a localized abdominal bruit to the left or right of the midline or in both locations . Coarctation of the aorta frequently causes a decreased blood pressure in the lower extremities relative to the arms, and/or delayed or absent femoral arterial pulses.Pheochromocytoma may cause abrupt hypertension accompanied by headache, palpitations, pale appearance, and excessive sweating (Marik *et al.,* 2007).

Hypertensive crisis

Severely elevated blood pressure (equal to or greater than a systolic 180 or diastolic of 110—sometimes termed malignant or accelerated hypertension) is referred to as a "hypertensive crisis", as blood pressure at this level confers a high risk of complications.

People with blood pressures in this range may have no symptoms, but are more likely to report headaches (22% of cases) and dizziness than the general population. Other symptoms accompanying a hypertensive crisis may include visual deterioration due to retinopathy, breathlessness due to heart failure, or a general feeling of malaise due to kidney failure. Most people with a hypertensive crisis are known to have elevated blood pressure, but additional triggers may have led to a sudden rise. A "hypertensive emergency" is diagnosed when there is evidence of direct damage to one or more organs as a result of severely elevated blood pressure greater than 180 systolic or 120 diastolic. This may include hypertensive encephalopathy, caused by brain swelling and dysfunction, and characterized by headaches and an altered level of consciousness . Retinal papilledema and/or fundal bleeds and exudates are another sign of target organ damage. Chest pain may indicate heart muscle damage or sometimes aortic dissection, the tearing of the inner wall of the aorta. Breathlessness, cough, and the coughing up of blood-stained sputum are characteristic signs of pulmonary edema, the swelling of lung tissue due to left ventricular failure an inability of the left ventricle of the heart to adequately pump blood from the lungs into the arterial system. Rapid deterioration of kidney function and microangiopathic hemolytic anemia may also occur. In these situations, rapid reduction of the blood pressure is mandated to stop ongoing organ damage. In contrast there is no evidence that blood pressure needs to be lowered rapidly in hypertensive urgencies where there is no evidence of target organ damage and over aggressive reduction of blood pressure is not without risks. Use of oral medications to lower the BP gradually over 24 to 48h is advocated in hypertensive urgencies.

CAUSES

Primary hypertension

Hypertension results from a complex interaction of genes and environmental factors. Numerous common genetic variants with small effects on blood pressure have been identified as well as some rare genetic variants with large effects on blood pressure, but the genetic basis of hypertension is still poorly understood.

Blood pressure rises with aging and the risk of becoming hypertensive in later life is considerable (Mesas *et al.,*2011). Several environmental factors influence blood pressure. High salt intake raises the blood pressure in salt sensitive individuals; lack of exercise, obesity, stress, and depression can play a role in individual cases. The possible role of other factors such as caffeine consumption and vitamin D deficiency (Lawlor and Smith, 2005) are less clear. Insulin resistance, which is common in obesity and is a component of syndrome X (or the metabolic syndrome), is also thought to contribute to hypertension. Events in early life, such as low birth weight, maternal smoking, and lack of breast feeding may be risk factors for adult essential hypertension, although the mechanisms linking these exposures to adult hypertension remain unclear (Grossman *et al.,*2012).

Secondary hypertension

Secondary hypertension results from an identifiable cause. Kidney disease is the most common secondary cause of hypertension. Hypertension can also be caused by endocrine conditions, such as Cushing's syndrome, hyperthyroidism, hypothyroidism, acromegaly, Conn's syndrome or hyperaldosteronism, hyperparathyroidism and pheochromocytoma.

Other causes of secondary hypertension include obesity, sleep apnea, pregnancy, coarctation of the aorta, excessive liquorice consumption and certain prescription medicines, herbal remedies and illegal drugs (Palatin et al.,2009).

Pathophysiology

In most people with established essential (primary) hypertension, increased resistance to blood flow accounts for the high pressure while cardiac output remains normal. There is evidence that some younger people with prehypertension or 'borderline hypertension' have high cardiac output, an elevated heart rate and normal peripheral resistance, termed hyperkinetic borderline hypertension. These individuals develop the typical features of established essential hypertension in later life as their cardiac output falls and peripheral resistance rises with age. Whether this pattern is typical of all people who ultimately develop hypertension is disputed. The increased peripheral resistance in established hypertension is mainly attributable to structural narrowing of small arteries and arterioles, although a reduction in the number or density of capillaries may also contribute. Whether increased active arteriolarvasoconstriction plays a role in established essential hypertension is unclear (Chobanian, 2007). Hypertension is also associated with decreased peripheral venous compliance which may increase venous return, increase cardiac preload and, ultimately, cause diastolic dysfunction.

Pulse pressure is frequently increased in older people with hypertension. This can mean that systolic pressure is abnormally high, but diastolic pressure may be normal or low — a condition termed isolated systolic hypertension. The high pulse pressure in elderly people with hypertension or isolated systolic hypertension is explained by increased arterial stiffness, which typically accompanies aging and may be exacerbated by high blood pressure (Esler *et al.*,2010).

Many mechanisms have been proposed to account for the rise in peripheral resistance in hypertension. Most evidence implicates either disturbances in the kidneys' salt and water handling (particularly abnormalities in the intrarenal renin-angiotensin system) and/or abnormalities of the sympathetic nervous system (Marchesi *et al.*, 2008). These mechanisms are not mutually exclusive and it is likely that both contribute to some extent in most cases of essential hypertension. It has also been suggested that endothelial dysfunction and vascular inflammationmay also contribute to increased peripheral resistance and vascular damage in hypertension. Interleukin 17 has garnered interest for its role in increasing the production of several other immune system chemical signals thought to be involved in hypertension such astumor necrosis factor alpha, interleukin 1, interleukin 6, and interleukin 8 (Padawal *et al.,*2009).

Diagnosis

Hypertension is diagnosed on the basis of a persistently high blood pressure. Traditionally, theNational Institute of Clinical Excellence recommends three separate sphygmomanometer measurements at one monthly intervals. The American Heart Association recommends at least three measurements on at least two separate health care visits (Kario, 2009). An exception to this is those with very high blood pressure readings especially when there is poor organ function (Franklin *et al.,*2012).

Initial assessment of the hypertensive people should include a complete history and physical examination. With the availability of 24-hour ambulatory blood pressure monitors and home blood pressuremachines, the importance of not wrongly diagnosing those who have white coat hypertension has led to a change in protocols. In the United Kingdom, current best practice is to follow up a single raised clinic reading with ambulatory measurement, or less ideally with home blood pressure monitoring over the course of 7 days. Pseudohypertension in the elderly or noncompressibility artery syndrome may also require consideration. This condition is believed to be due to calcification of the arteries resulting in abnormally high blood pressure readings with a blood pressure cuff while intra arterial measurements of blood pressure are normal. Orthostatic hypertension is when blood pressure increases upon standing.

Once the diagnosis of hypertension has been made, physicians will attempt to identify the underlying cause based on risk factors and other symptoms, if present. Secondary hypertension is more common in preadolescent children, with most cases caused by kidney disease. Primary or essential hypertension is more common in adolescents and has multiple risk factors, including obesity and a family history of hypertension. Laboratory tests can also be performed to identify possible causes of secondary hypertension, and to determine whether hypertension has caused damage to the heart, eyes, and kidneys. Additional tests for diabetes and high cholesterol levels are usually performed because these conditions are additional risk factors for the development of heart disease and may require treatment.

Serum creatinine is measured to assess for the presence of kidney disease, which can be either the cause or the result of hypertension. Serum creatinine alone may overestimate glomerular filtration rate and recent guidelines advocate the use of predictive equations such as the Modification of Diet in Renal Disease (MDRD) formula to estimate glomerular filtration rate (eGFR)(Mancia *et al.*,2007). eGFR can also provide a baseline measurement of kidney function that can be used to monitor for side effects of certain antihypertensive drugs on kidney function. Additionally, testing of urine samples for protein is used as a secondary indicator of kidney disease. Electrocardiogram (EKG/ECG) testing is done to check for evidence that the heart is under strain from high blood pressure. It may also show whether there is thickening of the heart muscle or whether the heart has experienced a prior minor disturbance such as a silent heart attack. A chest X-ray or an echocardiogram may also be performed to look for signs of heart enlargement or damage to the heart.

Prevention

Much of the disease burden of high blood pressure is experienced by people who are not labelled as hypertensive (Chiolero *et al.,* 2013). Consequently, population strategies are required to reduce the consequences of high blood pressure and reduce the need for antihypertensive drug therapy. Lifestyle changes are recommended to lower blood pressure, before starting drug therapy. The 2004 British Hypertension Society guidelines proposed the following lifestyle changes consistent with those outlined by the US National High BP Education Program in 2002 for the primary prevention of hypertension:

- maintain normal body weight for adults (e.g. body mass index 20–25 kg/m^2)
- reduce dietary sodium intake to <100 mmol/ day (<6 g of sodium chloride or <2.4 g of sodium per day)

- engage in regular aerobic physical activity such as brisk walking (≥30 min per day, most days of the week)
- limit alcohol consumption to no more than 3 units/day in men and no more than 2 units/day in women
- consume a diet rich in fruit and vegetables (e.g. at least five portions per day);

Effective lifestyle modification may lower blood pressure as much as an individual antihypertensive drug. Combinations of two or more lifestyle modifications can achieve even better results.

Management

Lifestyle modifications

The first line of treatment for hypertension is identical to the recommended preventive lifestyle changes (Go *et al.,* 2013) and includes dietary changes, physical exercise, and weight loss. These have all been shown to significantly reduce blood pressure in people with hypertension. Their potential effectiveness is similar to and at times exceeds a single medication. If hypertension is high enough to justify immediate use of medications, lifestyle changes are still recommended in conjunction with medication. Dietary change, such as a low sodium diet and a vegetarian diet are beneficial. A long term low sodium diet is effective in reducing blood pressure, both in people with hypertension and in people with normal blood pressure. Also, the DASH diet, a diet rich in nuts, whole grains, fish, poultry, fruit and vegetables lowers blood pressure. A major feature of the plan is limiting intake of sodium, although the diet is also rich in potassium, magnesium, calcium, as well as protein (Aburto *et al.*, 2013). A vegetarian diet is associated with a lower blood pressure and switching to such a diet may be useful for reducing high blood pressure. A diet high in potassium lowers blood pressure in those with high blood pressure and may improve outcomes in those with normal kidney function. Some programs aimed to reduce psychological stress such as biofeedback or transcendental meditation may be reasonable add-ons to other treatment to reduce hypertension. However several techniques, namely yoga, relaxation and other forms of meditation do not appear to reduce blood pressure (Nelson, 2010), and there are major methodological limitations with many studies of stress reduction techniques. There is no clear evidence that the modest reduction in blood pressure with stress reduction techniques results in prevention of cardiovascular disease.

Several exercise regimes—including isometric resistance exercise, aerobic exercise, resistance exercise, and device-guided breathing—may be useful in reducing blood pressure.

Medications

Several classes of medications, collectively referred to as antihypertensive medications, are available for treating hypertension. Use should take into account the person's cardiovascular risk as well as blood pressure readings, in order to gain a more accurate picture of the person's risks. Benefit of medications is related to a person's cardiac disease risk. Evidence for medications in those with mild hypertension (between 140/90 mmHg and 160/100 mmHg) and no other health problems is less clear with some reviews finding no benefit and other reviews finding benefit. Medications are not recommended for people with prehypertension or high normal blood pressure.

The best first line medication is disputed. The Cochrane collaboration, World Health Organization and the United States guidelines support low dose thiazide-based diuretic as first line treatment (Wiysonge *et al.,* 2012). The UK guidelines emphasise calcium channel blockers (CCB) in preference for people over the age of 55 years or if of African or Caribbean family origin, with angiotensin converting enzyme inhibitors (ACE-I) used first line for younger people. In Japan starting with any one of six classes of medications including: CCB, ACEI/ARB, thiazide diuretics, beta-blockers, and alpha-blockers is deemed reasonable, while in Canada and Europe all of these but alpha-blockers are recommended as options. When compared to placebo and other anti-hypertensive medications as first-line therapy for hypertension, beta-blockers have greater benefit in stroke reduction, but no difference on coronary heart disease or all-cause mortality (Sever *et al.,* 2011). However, three-quarters of active beta-blocker treatment in the randomised controlled trials included in the review were with atenolol and none with the newer vasodilating beta-blockers.

Medication combinations

The majority of people require more than one medication to control their hypertension. In those with a systolic blood pressure greater than 160 mmHg or a diastolic blood pressure greater than 100 mmHg the American Heart Association recommends starting both a thiazide and an ACEI, ARB or CCB. An ACEI and CCB combination can be used as well. Unacceptable combinations are non-dihydropyridine calcium blockers (such as verapamil or diltiazem) and beta-blockers, dual renin–angiotensin system blockade (e.g. angiotensin converting enzyme inhibitor + angiotensin receptor blocker), renin–angiotensin system blockers and beta-blockers, beta-blockers and centrally acting medications. Combinations of an *ACE-inhibitor* or a*ngiotensin II–receptor antagonist*, a *diuretic* and an *NSAID* (including selective COX-2 inhibitors and non-prescribed medications such as ibuprofen) should be avoided whenever possible due to a high documented risk of acute kidney failure. The combination is known colloquially as a "triple whammy" in the Australian health industry (Go *et al.*,2013). Tablets containing fixed combinations of two classes of medications are available and while convenient for the people, may be best reserved for those who have been established on the individual components. Additionally, the use of treatments with vasoactive agents for people with pulmonary hypertension with left heart disease or hypoxemic lung diseases may cause harm and unnecessary expense.

Elderly

Treating moderate to severe hypertension decreases death rates and cardiovascular morbidity and mortality in people aged 60 and older. The recommended BP goal is advised as <150/90 mm Hg with thiazide diuretic, CCB, ACEI, or ARB being the first line medication in the United States, and in the revised UK guidelines calcium-channel blockers are advocated as first line with targets of clinic readings <150/90, or <145/85 on ambulatory or home blood pressure monitoring. There are no randomized clinical trials addressing the goal blood pressure of hypertensives over 79 years old. A recent review concluded that antihypertensive treatment reduced cardiovascular deaths and disease, but did not significantly reduce total death rates. Two professional organizations have published guidelines for the management of hypertension in persons over 79 years old (Calhoun *et al.,*2008).

ERYTHROPOIETIN

Erythropoietin (**EPO**) is a glycoprotein hormone that controls erythropoiesis, or red blood cell production. It is a cytokine for erythrocyte precursors in the bone marrow. Human EPO has a molecular weight of 34 kDa.It is produced by interstitial fibroblasts in the kidney in close association with peritubular capillary and tubular epithelial tubule. It is also produced in perisinusoidal cells in the liver. While liver production predominates in the fetal and perinatal period, renal production is predominant during adulthood. In addition to erythropoiesis, erythropoietin also has other known biological functions. For example, it plays an important role in the brain's response to neuronal injury (Siren *et al.,*2001). EPO is also involved in the wound healing process (Haroon *et al.,*2003).

When exogenous EPO is used as a performance-enhancing drug, it is classified as an erythropoiesis-stimulating agent (ESA). Exogenous EPO can often be detected in blood, due to slight differences from the endogenous protein, for example, in features of posttranslational modification.

Function

Primary role in red blood cell production

Erythropoietin is an essential hormone for red cell production. Without it, definitive erythropoiesis does not take place. Under hypoxic conditions, the kidney will produce and secrete erythropoietin to increase the production of red blood cells by targeting CFU-E, proerythroblast and basophilic erythroblast subsets in the differentiation. Erythropoietin has its primary effect on red blood cell progenitors and precursors by promoting their survival through protecting these cells from apoptosis.

Erythropoietin is the primary erythropoietic factor that cooperates with various other growth factors (e.g., IL-3, IL-6, glucocorticoids, and SCF) involved in the development of erythroid lineage from multipotent progenitors. The burst-forming unit-erythroid (BFU-E) cells start erythropoietin receptor expression and are sensitive to erythropoietin. Subsequent stage, the colony-forming unit-erythroid (CFU-E), expresses maximal erythropoietin receptor density and is completely dependent on erythropoietin for further differentiation. Precursors of red cells, the proerythroblasts and basophilic erythroblasts also express erythropoietin receptor and are therefore affected by it.

Additional nonhematopoietic roles

Erythropoietin has a range of actions including vasoconstriction-dependent hypertension, stimulating angiogenesis, and inducing proliferation of smooth muscle fibers. It can increase iron absorption by suppressing the hormone hepcidin (Ashby *et al.,*2010).

EPO also affects neuronal protection during hypoxic conditions (stroke, etc.). Trials on human subjects are not yet reported; if proven to be a viable treatment of heart attack and stroke patients, it could improve the outcome and quality of life. The reasoning behind such a proposal is that EPO levels of 100 times the baseline have been detected in brain tissue as a natural response to (primarily) hypoxic damage.

Multiple studies have suggested that EPO improves memory. This effect is independent of its effect on hematocrit (Miskowiak et al., 2007).

Rather, it is associated with an increase in hippocampal response and effects on synaptic connectivity, neuronal plasticity, and memory-related neural networks (Adamcio e*t al.,* 2008; Adamcio *et al.,* 2010). EPO may also be an effective treatment for depression (Miskowiak *et al.,* 2009).

Mechanism of action

Erythropoietin has been shown to exert its effects by binding to the erythropoietin receptor (EpoR).EPO is highly glycosylated (40% of total molecular weight), with half-life in blood around five hours. EPO's half-life may vary between endogenous and various recombinant versions. Additional glycosylation or other alterations of EPO via recombinant technology have led to the increase of EPO's stability in blood (thus requiring less frequent injections). EPO binds to the erythropoietin receptor on the red cell progenitor surface and activates a JAK2 signaling cascade. Erythropoietin receptor expression is found in a number of tissues, such as bone marrow and peripheral/central nervous tissue. In the bloodstream, red cells themselves do not express erythropoietin receptor, so cannot respond to EPO. However, indirect dependence of red cell longevity in the blood on plasma erythropoietin levels has been reported, a process termed neocytolysis.

Synthesis and regulation

Erythropoietin levels in blood are quite low in the absence of anemia, at around 10 mU/ml. However, in hypoxic stress, EPO production may increase 1000-fold, reaching 10,000 mU/ml of blood. EPO is produced mainly by peritubular capillary lining cells of the renal cortex, which are highly specialized, epithelial-like cells. It is synthesized by renal peritubular cells in adults, with a small amount being produced in the liver. Regulation is believed to rely on a feedback mechanism measuring blood oxygenation (Jelkman, 2007). Constitutively synthesized transcription factors for EPO, known as hypoxia-inducible factors, are hydroxylated and proteosomally digested in the presence of oxygen.

Medical uses

Erythropoietins available for use as therapeutic agents are produced by recombinant DNA technology in cell culture, and include Epogen/Procrit (epoetin alfa) and Aranesp (darbepoetin alfa); they are used in treating anemia resulting from chronic kidney disease, inflammatory bowel disease (Liu *et al.*,2013) and myelodysplasia from the treatment of cancer, but include boxed warnings of increased risk of death, myocardial infarction, stroke, venous thromboembolism, tumor recurrence, and other severe off-target effects.

Pulmonary Hypertension and Erythropoietin

Uremia affects the lung with pathological alterations that worsen, as the disease progresses.Particularly noteworthy are anomalies in the transport of respiratory gases, alterations in diffusive mechanisms, diminution in ventilatory processes at rest, and functional alterations in the respiratory muscles.These patients, moreover, almost always present a significantly higher cardiac ejection fraction, low hemoglobin and hematocrit levels, and an increase in the pulmonary arterialpressure (PAP). The PAP usually tends to normalize, whenever arteriovenous fistula closure is undertaken, e.g., when the patient undergoes renal transplantation(Drueke *et al*.,2006).

Chronic hypoxia elicits a number of physiological responses that result in PH. Hypoxia causes active pulmonary vasoconstriction as well as a structural remodeling of the pulmonary arterial vasculature. Both of these responses diminish the luminal diameter of the small pulmonary arteries, increasing vascular resistance and contributing to the development of PH .

BP Response To Epo Administration in Humans

Normal Subjects

Importantly, Epo-induced increases in Haematocrit to approximately 49% in normotensive subjects were reported to be associated with a significant increase in resting mean arterial pressure (MAP) of 6 mmHg when measured by intra-arterial catheter , whereas a study using cuff measurements identified a significant exercise-induced increase in mean arterial pressure, while the nominal increase in resting BP was nonsignificant .The effect of Epo on BP in normal humans is independent of its effect on red blood cell volume. Both Epo-induced and transfusion- induced increases in Hct, or red blood cell volume, apparently do not change total blood volume significantly, because the increase in red blood cell volume is accompanied by a quantitatively similar decrease in plasma volume, resulting in a nearly constant blood volume. However, the BP response differs markedly: BP is reported to increase significantly in response to Epo, and to decrease after transfusions, despite similar increases in Haematocrit . In addition, Epo-induced hypertension cannot be readily explained by higher blood viscosity because this parameter increases similarly after both Epo (Furuland *et al.*,2005) and blood transfusions.This Hct- and blood viscosity-independent effect of Epo on BP may be caused by arterial vasoconstriction, as was demonstrated *in vitro* in rat renal and mesenteric arterioles and in human placental arteries and veins. Conceivably, if applicable to the human glomerular afferent arteriole, such a tension-increasingeffect of Epo might explain the persistent hyporeninemic hypoaldosteronism during Epo-induced hypertension reported in normal subjects, which was independent of changes in blood volume . However, evaluation of a true negative-feedback mechanism of Epo on renin production has not yet been reported.Thus, a subtle decrease in plasma and blood volume could result from either Epo-induced vasoconstriction or Epo-induced hyporeninemic hypoaldosteronism. In fact, hypertension and/or hypoaldosteronism could explain the transient natriuresis/chloruresis observed during Epo administration, and this might explain, at least in part, the decrease in plasma volume associated with Epo-induced increases in red cell volume.In contrast to *in vitro* and animal studies, Epo-induced vasoconstriction in human arteries is poorly characterized, but can be prevented *in vitro* by AT1-receptor antagonism . In rat renal arterioles, the constrictive effect of Epo persisted after endothelium removal and indomethacin exposure, seemingly circumventing any direct role for endothelin, prostanoids, or nitric oxide . Nevertheless, in both normal subjects and predialysis CKD subjects, an acute Epo injection was found to significantly impair endothelium-dependent vasodilation as evidenced by an attenuated forearm blood flow response to methacholine.

Dissociation of Epo's Effect on BP from its Erythropoietic Effect

The clinical observation that Epo-induced hypertension is independent of its effect on red blood cell mass and viscosity is supported by the experimental demonstration in rats that coadministration of Epo with either a synthetic Epobinding protein or an anti-Epo antibody prevented Epo-induced hypertension while preserving the erythropoietic response.This suggests the interesting possibility that different epitopes on the erythropoietin protein confer independent erythropoietic and hemodynamic effects.

Epo's Effects on Vascular Endothelin (ET) and Endothelial Prostanoids

Epo induces ET-1 release and produces an enhanced mitogenic response in endothelial cells .Production of the vasodilating prostaglandin PGI2 (prostacyclin) is decreased and the vasoconstricting prostanoid TXB2 (thromboxane) is increased .These results suggest an important role of ET-1 and the altered balance between vasodilating and vasocon-474 stricting prostanoids in modulating Epo-induced vasoconstriction . However, *in vivo* data do not directly support a role for ET-1, as plasma levels in nephrectomized rats did not rise with Epo administration, despite Epo-induced hypertension . However, effects on tissue ET-1 expression and renal ET-1 production with subsequent effects on renal sodium transport are not excluded.

Epo's Effects on NITRIC OXIDE (NO)

Epo-induced polycythemia has been shown to increase renal NO production in rats based on urinary cGMP or NO3 excretion rates, but it is unclear whether the effect is secondary to high Epo levels and/or the raised hematocrit. Increased NO production is important in limiting the hypertensive response to Epo/polycythemia because inhibition of NO production by l-NAME increases the BP observed in Epo treated rats. However, as expected from the results of other studies, Epo also provides an obvious NO-independent hypertensinogenic effect.

In contrast, in human endothelial cells, Epo was demonstrated to decrease eNOS expression, which would be expected to result in decreased endothelial NO production. The mechanism is not fully elucidated but may include increased production of reactive oxygen species and asymmetric dimethylarginine, which decrease endothelial NO production. These seemingly disparate findings might be explained by differing effects of Epo on systemic and renal NO production. An extrarenal or systemic effect to blunt endothelial NO production, combined with the increased ET-1 response and predominance of thromboxane over prostacyclin could explain the Epo-induced vasoconstrictive effect. The effect of Epo to increase renal NO production could be the consequence of the increase in ET-1 production, which is a well characterized stimulus for renal NO production. ET-1-induced renal NO production inhibits collecting duct sodium reabsorption in sufficient magnitude to lower BP in mice , conferring a potential counter-regulatory mechanism against Epo-induced hypertension and perhaps partially explaining the hypertensive response to l-NAME in Epo-treated rats and rabbits. Because the renal effect is likely to be less important for BP control in patients with more advanced GFR reduction, such patients may be more predisposed to hypertension. In addition to inhibition of extrarenal eNOS/NO production, there is evidence that Epo treatment can impair NO action. Chronic Epo treatment is reported to impair the vasodilatory response to endothelial NO and, in nephrectomized rats, is associated with an abrogated cGMP generation response to NO donors *in vitro*.

In summary, the net effect of Epo-induced changes in NO production/action are difficult to predict for the *in vivo* situation.The direction and magnitude of Epo-induced BP changes might be the consequence of its vasoconstrictive effect, caused both by decreased systemic NO production and resistance to NO vasodilation. This effect is likely to be modulated by a potential ET-1/NO-induced hypotensive effect mediated by inhibition of collecting duct sodium and water reabsorption.This latter effect may, however, be counteracted by Epo itself, which when administered to the isolated perfused rat kidney, induces sodium retention by a renin-angiotensin II-mediated mechanism .

Pathophysiology of Epo-Induced Hypertension in Predialysis CKD Patients

One uncontrolled study in 48 predialysis patients using home BP readings reported a significant 7 mmHg increase in SBP after prolonged Epo administration, with no significant changes in DBP. In another study, Hct increased from 21 to27% in association with increased total peripheral resistance (TPR) in parallel with a comparable percentage increase in blood volume but with no change in GFR, RPF, or cardiac index (CI). Rheological effects of Epo administration, examined in another uncontrolled predialysis study, showed a significant increase in blood viscosity, TPR, and BP increases requiring increased anti-hypertensive medication use, but the authors acknowledged the difficulty in attributing BP elevations to increased viscosity (Furuland *et al*.,2005). Endothelial vasorelaxation is also affected by Epo in this population, inasmuch as IV Epo administration to predialysis patients induced a significant reduction in endothelium-dependent vasodilation as noted above. This finding is strong evidence that Epo reduces NO production or action in the endothelium *in vivo* and is consistent with *in vitro* data in human endothelial cells showing that Epo impairs NO production and eNOS expression .

No Difference in BP Response Between Darbepoetin or Epo in Predialysis Patients

Hypertension was similar in Epo and darbepoetin arms in both trials (Locatelli *et al.*, 2001). Not surprisingly, similar hypertensive effects in predialysis patients have been reported for pharmacologic administration of the newer ESA agents, pegylated Epo and hematide, which share Epo's mechanism of activating the Epo receptor (Macdougal *et al*., 2008).

In both dialysis and predialysis patients, "replacement levels" of Epo are insufficient treatment for renal anemia, and current therapy with Epo results in a highly superphysiologic plasma Epo concentration profile over time. After an IV dose, plasma levels rise rapidly to 500 times basal levels and then decline rapidly during the treatment cycle. Even with the newer long half-life ESAs (*e.g.*, darbepoetin and pegylated Epo), a substantial portion of the interdosing interval, as practiced, exhibits highly supraphysiologic plasma levels with respect to Epo receptor agonism. Whether dosing that targets a more constant and near-physiologic plasma ESA concentration profile might mitigate hypertension in humans or animal models has not been reported. Accordingly, future treatments of renal anemia that do not exhibit Epo receptor agonism (*e.g.*, agents that might improve iron transport and/or reduce inflammatory signaling in the presence of modest Epo levels) might circumvent Epo-induced hypertension completely.

Pathophysiology of Epo-Induced Hypertension in Hemodialyzed Patients

The best studied and most likely mechanisms by which Epo induces hypertension in hemodialyzed patients comprise changes in hemodynamics and activation of vasoactive hormone axes, namely enhanced adrenergic sensitivity and increased circulating endothelin-1 levels.

Role of Enhanced Noradrenergic and Angiotensin II Sensitivity and ET-1 in Epo-Induced Hypertension

At least a subset of hemodialyzed patients exhibit an accentuated increase in the BP response to angiotensin II infusion during Epo treatment as compared with the pre-Epo condition . This apparent hypersensitivity to angiotensin II correlated with the magnitude of the Epo-induced increase in BP. In addition, hemodialyzed subjects with Epo-induced hypertension also exhibit *noradrenergic* hypersensitivity . TPR increased significantly, and CI decreased, albeit moderately and nonsignificantly. In addition to the increased noradrenergic sensitivity, plasma norepinephrine concentration was reported to increase significantly after 12 wk of Epo treatment in normotensive hemodialysis patients, paralleled by a significant increase in MAP, from 93 to 97 mmHg.Pursuant to the finding of increased sympathetic signaling, 2-receptor density in white blood cells was highly elevated before Epo and was significantly reduced by Epo treatment in hemodialyzed patients exhibiting a significant rise in MAP (12 mmHg) (Muller *et al*.,2009). Thus, if reduction in receptor density reflects improved sympathetic signaling in arterioles, it is possible that Epo induces a supernormal increase in 2 functioning relative to that with transfusion, thereby leading to hypertension. Several studies have found that Epo-induced hypertension in hemodialyzed patients was associated with significantly increased circulating ET-1 concentrations (Stefanidis *et al*.,2001) and that the accentuated ET-1 response to Epo was particularly great in the patients who exhibited the highest pressure response to Epo . In contrast to angiotensin II and norepinephrine, however, no ET-1 hypersensitivity was found, as evidenced by the similar changes in forearm resistance in response to ET-1 infusions with and without Epo . Thus, Epo-induced hypersensitivity to angiotensin II and norepinephrine, as well as increased ET-1 activity, are reasonable mechanisms for Epo-induced hypertension in hemodialyzed ESRD patients.

CONCLUSION

Hypertension is a public health disease whic is increasing at an alarming rate.It occurs mostly in the elderly but theses days can occur at any age bracket.It is a major health concern both to the developing and developed contries in the World. Hypertension is a chronic medical condition in which the blood pressure in the arteries is elevated. Normal blood pressure at rest is within the range of 100–140 mmHg systolic and 60–90 mmHg diastolic. Hypertension is present if the blood pressure is persistently at or above 140/90 (mmHg).Hypertension mostly affect the kidneys of the patients which affect synthesis and release of erythropoietin and will affect both the erythropoiesis leading to anaemia and other non-erythropoietic functions of erythropoietin.The paper is a review on erythropoietin in hypertension.

Uremia affects the lung with pathological alterations that worsen, as the disease progresses. Hypoxia causes active pulmonary vasoconstriction as well as a structural remodeling of the pulmonary arterial vasculature. Both of these responses diminish the luminal diameter of the small pulmonary arteries, increasing vascular resistance and contributing to the development of pulmonary hypertension .

The level of erythropoietin should be monitored carefully during treatment to prevent excrutiating hypertension.

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