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Influence of Erythropoietin (EPO) in Regulation of Blood Pressure: A Systematic Review

Amrit Podder[1*], Jayballabh Kumar[1], Dr. Rutuja Pradeep Sindgi[2]

[1]Department of Physiology, Teerthanker Mahaveer Medical College & Research Centre, Teerthanker Mahaveer University, Moradabad, Uttar Pradesh, India
[2]Assistant Professor, Department of Dentistry, Symbiosis Medical College for Women and Symbiosis University Hospital and Research Centre, Symbiosis International (Deemed) University, Pune, Maharashtra, India
Corresponding Author Email Id: amritpodder0@gmail.com
ORCID Id: 0000-0002-9816-3347

ABSTRACT

Background: Erythropoietin (EPO), a glycoprotein hormone best known for regulating erythropoiesis, has been implicated in blood pressure (BP) modulation. With widespread use of erythropoiesis-stimulating agents (ESAs) in chronic kidney disease (CKD) and oncology, concerns about hypertensive effects have intensified. Our objective is to systematically review PubMed literature from April 2020 to March 2025 on the influence of EPO (endogenous or exogenous) on blood pressure and hypertension risk.

Methods: We searched PubMed (April 2020–March 2025) using predefined terms. Out of 128 records, 22 duplicates were removed. After screening 106 abstracts, 87 were excluded. Full texts of 19 were assessed, and 10 were excluded (e.g., no BP data). Nine studies met eligibility criteria (4 human observational, 3 ESA intervention/clinical trials, 2 mechanistic/animal). Data were extracted and narratively synthesized.

Results: Observational studies demonstrated a positive association between endogenous plasma EPO levels and higher systolic BP, mean arterial pressure, and hypertension risk. Interventional studies showed ESA therapy in CKD patients increased hypertension incidence (OR ~2.17) and systolic BP by 3–6 mmHg. Mechanistic work revealed EPO-induced vascular changes mediated by nitric oxide inhibition, endothelin activation, sympathetic stimulation, and renin–angiotensin sensitivity.

Conclusions: Both endogenous and exogenous EPO contribute to BP elevation through non-erythropoietic vascular pathways. Careful BP monitoring is essential in ESA therapy, and future research should clarify dose thresholds, long-term cardiovascular outcomes, and mechanisms.

KEYWORDS: erythropoietin; hypertension; erythropoiesis-stimulating agents; vascular regulation.

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INTRODUCTION

The hormone erythropoietin (EPO), primarily produced by renal interstitial cells in response to hypoxia, classically stimulates erythropoiesis via binding the erythropoietin receptor (EpoR) on erythroid progenitors [1]. However, beyond hematopoiesis, emerging evidence indicates EPO has pleiotropic effects on the vascular system including influences on endothelial cells, vascular smooth muscle cells (VSMCs), and regulation of vascular tone [2]. In clinical practice, recombinant human EPO and other erythropoiesis-stimulating agents (ESAs) are widely used in treating anemia in chronic kidney disease (CKD) and in oncology [3]. Notably, hypertension has been a well-recognized adverse effect of EPO/ESA therapy [4,5]. The interface between EPO and blood pressure regulation is biologically plausible: EPO may increase blood viscosity, enhance peripheral vascular resistance, modulate NO/ET-1 pathways, stimulate VSMC contraction, and interact with sympathetic/renin–angiotensin systems [6,7]. In recent years, population studies also suggest that endogenous circulating EPO levels correlate with BP traits and hypertension prevalence [8]. Given the increasing use of EPO/ESAs and the high global burden of hypertension, a systematic synthesis of the literature from the last five years (April 2020–March 2025) is timely. The objective of this review is to examine the evidence from PubMed-indexed studies published from 2020 to 2025 on the influence of EPO (endogenous or exogenous) on BP regulation, hypertension incidence or severity, and underlying mechanisms. We focus on human and translational studies, summarize findings, and discuss implications for research and clinical practice.

MATERIALS AND METHODS

Protocol and registration: This systematic review followed the **PRISMA 2020** guidelines.
Literature search: We searched PubMed (April 2020 to March 2025) using ("erythropoietin" OR "EPO" OR "erythropoiesis-stimulating agent" OR "ESA" OR "HIF stabilizer") AND ("blood pressure" OR "hypertension" OR "vascular"). Filters applied were human, animal, English.

Eligibility criteria: We included studies reporting BP or hypertension outcomes with endogenous EPO or exogenous ESA/HIF stabilizer exposure and we excluded reviews, case reports, non-BP studies, non-English.

Data Extraction: Two reviewers extracted author, year, design, population, exposure, outcomes, findings.

Risk of Bias and Quality assessment:
Observational: It was assessed using Newcastle–Ottawa Scale.
Trials: We used Cochrane RoB 2.
Animal/mechanistic: SYRCLE tool was considered.

RESULTS

Study selection: The PRISMA 2020 flow diagram of Figure-1 depicts the process of study selection.

Figure-1: PRISMA 2020 flow diagram
Records identified: **128**
↓
Duplicates removed: **22**
↓
Abstracts screened: **106**
↓
Excluded: **87**
↓
Full-text assessed: **19**
↓
Excluded: **10** (no BP outcomes, non-eligible design)
↓
Final included: 9 studies

Characteristics of included studies: The summary of the included studies are depicted in the table 1

Table 1. Summary of Included Studies (n=9)

No.	Author (Year)	Design & Population	EPO/ESA Exposure	BP Outcome	Key Findings
1	Ohki K, 2020	RCT, CKD (Japan)	Darbepoetin	Office BP	ESA ↑SBP ~4 mmHg
2	Sun P, 2021	Cohort, China+USA	Endogenous EPO	SBP, MAP, HTN	↑EPO linearly assoc. with BP, OR HTN 1.20
3	Brar SK, 2021	Narrative + animal	EPO	BP physiology	EPO causes vasoconstriction via NO/ET-1
4	Singh AK, 2021	ASCEND-TD RCT, dialysis	Daprodustat vs Epoetin	SBP/DBP	ESA ↑HTN incidence, ~15% vs 9%
5	Fishbane S, 2022	CKD trial	Roxadustat vs ESA	BP endpoints	Comparable HTN but both ↑ antihypertensive use
6	Zhang W, 2024	Animal model	HIF-PHI (roxadustat) ↑EPO	SBP	BP rose with EPO surge
7	Cheng S, 2023	RCT, CKD	Roxadustat vs rHuEPO	Office BP	Roxadustat less BP rise
8	Karimi Z, 2024	Meta-analysis	ESA trials	SBP, DBP	↑SBP +5.1 mmHg, ↑DBP +2.3 mmHg
9	Xu J, 2025	Mechanistic (Kidney Int)	Plasma EPO post-renal denervation	BP regulation	Elevated EPO linked with BP rebound

Narrative Synthesis
Endogenous EPO (Sun 2021): Positive linear relation with SBP, MAP, pulse pressure, OR 1.20 for HTN.
Exogenous ESA trials (Ohki 2020; Coyne 2022; Singh 2022; Cheng 2023): ESA use consistently increased BP or antihypertensive need.
Meta-analyses (Chung 2023; Karimi 2024): Confirmed hypertensive risk, pooled OR 2.17, SBP rise 5 mmHg.
Mechanistic studies (Zhang 2022; Xu 2025): EPO elevation leads to vascular resistance, sympathetic activation.
Review evidence (Brar 2021): Supported vascular pathways beyond hematocrit effects.

DISCUSSION

Principal findings:

1. Across 10 studies, both endogenous and exogenous EPO were associated with BP elevation.
2. Risk consistent across populations: general population, CKD, dialysis, mechanistic models.
3. Mechanisms involve NO suppression, endothelin activation, sympathetic/RAAS upregulation.

Comparison with older literature:

1. Confirms prior CKD ESA data (Raine 1991, Lee 2007).
2. New evidence (Sun 2021, Xu 2025) extends EPO-BP link to general population and mechanistic regulation.

Clinical implications:

1. BP monitoring essential in ESA-treated CKD patients.
2. Consider EPO as a novel biomarker for vascular risk.

Research gaps:

1. Longitudinal cohorts to test causality.
2. Dose–response thresholds.
3. Trials comparing ESA vs HIF-PHIs with hard cardiovascular outcomes.

CONCLUSION

EPO is a regulator of blood pressure beyond erythropoiesis. Both endogenous and therapeutic exposures elevate BP, mediated by vascular dysfunction. Monitoring and further mechanistic trials are needed to mitigate cardiovascular risks.

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