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REVIEW

Effects of drugs on the oxygen dissociation curve—a scoping review

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Abstract

Purpose The shape and position of the hemoglobin-oxygen dissociation curve (ODC) is of critical importance in medicine, as it determines the uptake of O_2 in the lungs and the delivery of O_2 to the tissues. Numerous reports have identified affinity-modulating effects of drugs in humans. Such effects may be relevant to conditions such as pulmonary diffusion disorders, peripheral vascular disease, or coronary artery disease. The aim of this scoping review was to assess and summarize the current evidence on these effects.

Methods The review was based on the PRISMA-ScR guidelines. We searched PubMed and the Cochrane Library and only included papers with free full-text access. The search covers all papers published before September 2024 and used the following keywords: "Oxygen affinity" or "oxygen dissociation curve" in combination with > 100 substance classes that should cover most drugs in clinical use.

Results The search returned 2447 hits of which 80 were selected for further full text review. In terms of discipline, cardiology accounted for the largest proportion, and in terms of effect quality, a right-ward shift resulting in improved tissue oxygenation was most common. For example, quantitative data show an increase in P_{50} of 6.1–12.4% and 25–53% for propranolol and RSR13, respectively.

Conclusion Despite a substantial body of data, the effects of the vast majority of drugs on the ODC have not been studied or have not been studied in sufficient detail. The undeniable potential for medical interventions to alter the ODC calls for revival of this area of research.

Keywords Pharmaceuticals · Hemoglobin · Oxygen affinity · Half saturation pressure · P_{50}

Abbreviations

2,3-BPG	2,3-Bisphosphoglycerate
Hb	Hemoglobin
ODC	Oxygen dissociation curve
SO_2	Oxygen saturation

Introduction

Oxygen transport to our tissues consists of two convective and two diffusive pathways connected in series: alveolar ventilation (convection), O_2 diffusion across the alveolar-capillary membrane, blood flow to the microcirculation (convection), and finally diffusion of O_2 into the cell's furnaces, the mitochondria. Thus, total oxygen supply to cells is critically dependent on all 4 processes, with the reversible binding of oxygen to hemoglobin (Hb) receiving probably the most attention in the history of blood and respiratory physiology. This reversible binding was first observed by Stokes in 1864 [1], long before the sigmoidal shape of the oxygen dissociation was reported by Bohr et al. in 1904 [2]. Nearly a decade later, an idea of the puzzling reason for this non-linear shape, namely, some kind of cooperative behavior in O_2 binding between Hb subunits, first came up with the work of A.V. Hill in 1913 [3] and was then confirmed by numerous experimental work that followed in the course of the century. Some

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allosteric modulators of the oxygen dissociation curve (ODC) were already known at that time: CO_2 (by Bohr, Hasselbalch, and Krogh in 1904 [2]), H^+ (by Barcroft and Orbeli in 1910 [4]), and temperature (Barcroft and King in 1909 [5]). A fourth and most potent, 2,3-bisphosphoglycerate (2,3-BPG), was discovered almost half a century later and almost simultaneously by Benesch and Benesch in 1967 [6] and Chanutin and Curnish in the same year [7]. 2,3-BPG, produced in the Rapoport-Lübering bypass of glycolysis in red blood cells, is a major regulator of oxygen release by Hb. All of these four parameters shift the ODC to the right, meaning that Hb loses its affinity to interact with O_2 as it passes through a metabolically active tissue.

The shape and position of the ODC are undoubtedly of utmost importance in physiology [8]. In the steep part of the curve, there is efficient unloading of O_2 from Hb with respect to small changes in tissue PO_2, whereas in the flat, asymptotic part, which is characteristic of the gas situation in the lung, O_2 binding is almost independent of PO_2. Any change in the position of the ODC will therefore profoundly alter O_2 supply to the cells and O_2 uptake in the lungs, at the same time, although differently: A left-shifted curve facilitates O_2 binding whenever alveolar PO_2 is reduced but impairs O_2 delivery to the cells. A right-shifted curve improves tissue oxygenation but may be limiting O_2 uptake in the lungs. A quantitative measure of the position of the ODC is the P_{50}, the partial pressure of O_2 at 50% O_2 saturation of Hb. A measure of the steepness of the ODC around its P_{50} is the Hill coefficient *n*, defined as log (SO_2/1-SO_2)/log PO_2. The higher this ratio, the higher the degree of cooperativity between the four subunits of the tetrameric Hb molecule in terms of O_2 binding. In other words, the higher *n*, the more sensitive is Hb oxygenation/deoxygenation to PO_2 at low oxygen regimes.

The issue of left- versus right-shifted ODCs has been debated for long, and the benefits of either position in special situations, such as high-altitude stays, are still unresolved [9]. Moreover, given the enormous impact of modulating oxygen delivery to a critically ill patient suffering from respiratory failure (supply) or tissue hypoxia (demand), it is remarkable that this issue has barely found its way into medical research or practice. It was during the COVID pandemic that Böning et al. published a paper that critically addressed the urge to identify affinity modulating drugs to cope with an aggravated O_2 situation, especially in SARS-CoV-2 infected patients [10, 11]. In addition, in all situations of oxygen delivery deficiency, such as hypoxemia, pulmonary diffusion disorders, peripheral and central arterial diseases, coronary artery disease, and various forms of tissue ischemia, the ODC and its intended or accidental manipulation by administered drugs may play an underestimated role in clinical practice.

The aim of this scoping review was therefore to evaluate and summarize the current knowledge on the effects of various drugs on the ODC. This topic has not yet been systematically summarized but consists of a number of highly fragmented and mostly outdated reports and casual references. The review was designed as a scoping review based on the PRISMA-ScR guidelines, as introduced by Tricco et al. [12].

Methods

Data sources

PubMed and the Cochrane Library were used for the search process. To be considered for this review, papers had to meet the following criteria: They are available in at least one of two online directories, the language is English or German, and a full-text version is available through our institutional subscriptions (see limitations). Studies that did not provide sufficient information or consisted only of an abstract were excluded. If a study was considered unusable due to other reasons, it was noted in our documents. The first search was performed in July 2023 and the last one in September 2024. There were no restrictions regarding the publication date of a study.

Study selection

First, the search terms were defined. The drugs included in the search were obtained from the German website "Gelbe Liste Pharmindex," a database for medicine and pharmacology. The search terms for all drugs were then grouped into drug classes, such as "ACE-Inhibitors." Drug classes were used because a search for the trade names of pharmaceuticals would probably be unmanageable. The drug classes screened are listed in Table 1. All search processes were performed in the same, stereotypical way, namely, [1] and [2], where [1] was either "oxygen affinity" in title and/or abstract or "oxygen dissociation curve" in title and/or abstract. These two terms seemed to be the most appropriate to find studies on drug effects on the ODC. We validated the search strategy by comparing the retrievals with a handful of papers on ODC modulators that we had already collected in the past. Number [2] were the substance classes mentioned above. All different combinations were used in both databases, PubMed and Cochrane Library. The search performed in this way resulted in 2447 hits, which were entered into an Excel spreadsheet containing, among other entries, the date of the search, the database that provided the result, the combination of search terms used, and the number of results which were provided by the database. The actual sighting started with an exclusion by title followed by an exclusion by abstract.

Table 1 Substance classes used for the systematic search. Substance classes were taken from the website "Gelbe Liste Pharmindex"

ACE Inhibitors	Biguanides	Heparines	Proton Pump Inhibitors
Alcylating Agents	Bisphosphonates	Cardiac Glycosides	RAAS Inhibitors
Antibiotics	BRAF Inhibitors	Hirudines	Reverse Transcriptase Inhibitors
Analgetics	Tyrosinkinase Inhibitorss	Anti-HIV Drugs	Thyroid Hormones
Androgens	Calcineurin Inhibitors	Hormon Contraceptives	Loop Diuretics
Angiogenesis Inhibitors	Ca-Channel Blockers	Immune Modulators	SERDs
Anthracycline	CAR-T-Cell drugs	Immune Suppressors	SERMs
Antiarrythmics	CDK4/6 Inhibitors	Insuline	SNDRIs
Anticholinergics	Checkpoint Inhibitors	Interferones	SPRMs
Antidepressants	DOACs	JAK Inhibitors	SSRIs
Antidiabetics	Ditanes	K-Sparing Diuretics	SNRIs
Antiemetics	Diuretics	Kinase Inhibitors	Setrones
Anticonvulsant Drugs	DMARDs	KRAS Inhibitors	SGLT2 Inhibitors
Antigestagenes	Entry Inhibitors	Lipid Reducers	Statines
Antihistaminic Drugs	Estrogens	Levodopa	Taxanes
Antihypertensive Drugs	Expectorants	MAO Inhibitors	Thalidomid Analoges
Anticoagulants	Fibrates	MEK Inhibitors	Thiazides
Antimetabloites	Fibrinolytics	Monoclonal Antibodies	Anti-Platelet Drugs
Antimycotics	CGRP Receptor Antagonists	Narcotics	Thyreostatics
Antipsychotics	Gestagenes	Non-Opioid Analgetics	TNF_{α}-Inhibitors
Antitussives	Glinides	NSAR	TopoisomeraseI Inhibitors
Aromatase Inhibitors	Gliptides	Opioid Analgetics	TopoisomeraseII Inhibitors
AT2 Antagonists	GLP1 Receptor Antagonists	PARP Inhibitors	Triptanes
Barbiturates	Glucocorticoids	PCSK9 Inhibitors	Tricyclic Antidepressants
Benzodiazepines	GnRH Antagonists	PDE4 Inhibitors	Vinca Alkaloids
Beta Antagonists	H1 Antihistaminics	PDE5 Inhibitors	Vit.K Antagonists
Beta Blockers	H2 Antihistaminics	Proteasome Inhibitors	Z-Drugs

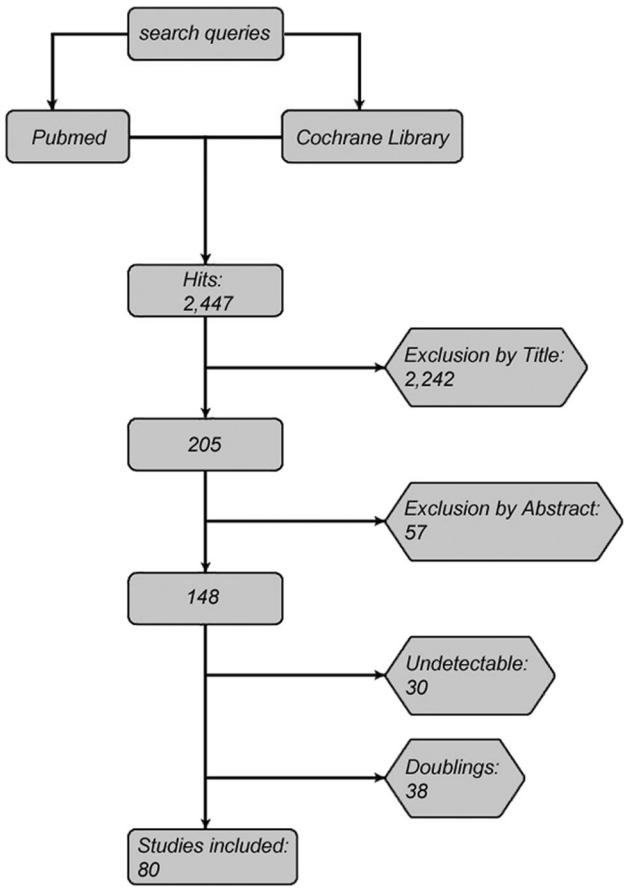

Fig. 1 Flowchart of the stereotypical search query

The former significantly reduced the number of potentially eligible papers to 205. Of the remaining studies, 57 were excluded by abstract. Doubtful cases were discussed among all authors. Of the remaining 148 studies, 30 studies had to be excluded because they were out of reach. In addition, 38 studies were in duplicate. After this process, 80 studies remained for full-text review. The flowchart in Fig. 1 illustrates the whole process. Finally, studies were then grouped according to the field of specialization in which the investigated drug is mainly used (Tables 2, 3, 4, and 5).

Results

Characteristics of sources of evidence

Time range: The distribution of studies by date of publication is shown in Fig. 2. Interestingly, the majority of them were published between 1970 and 1989. In later years, the numbers decreased. Our search query returned no results for the period before 1960 (see "Discussion"). Disciplines: The included studies were grouped according to the disciplines in which the drugs are mainly used (Fig. 2). Cardiology is clearly ahead of all other disciplines, followed by anaesthesiology and endocrinology. Some of the drugs are not associated with a certain discipline ("unclassified"). That is mostly the case when they are still in the early stages of testing, not yet on the market, or no longer in use. Test organisms: The vast majority of studies were conducted on humans, followed

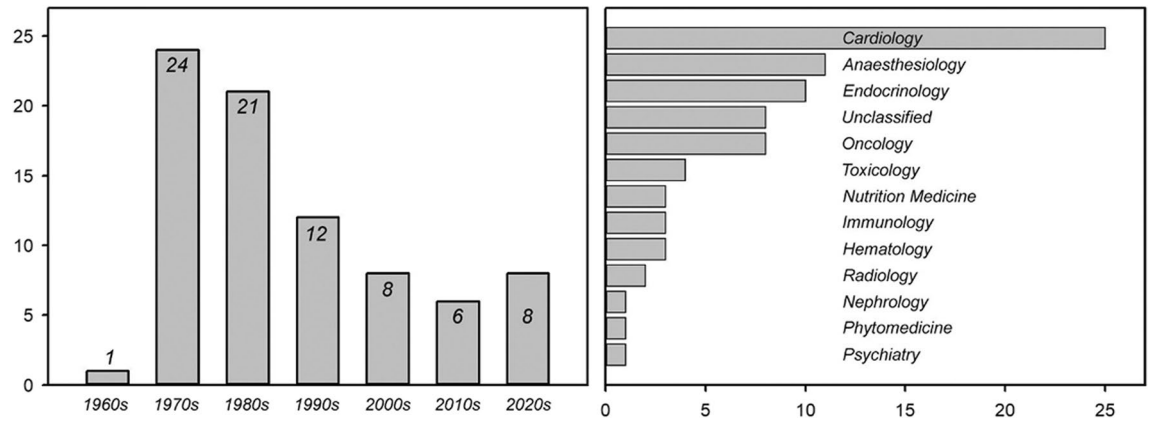

Fig. 2 Number of studies by decade (left) and by discipline (right)

by rats and dogs (Fig. 3). A notable proportion of five studies did not specify the test organism. Test setting: In vivo studies dominate but are roughly balanced with in vitro approaches (Fig. 3). A surprising number of five studies did not specify their approach at all. Sex distribution: Of the 80 studies reviewed, only 24 provided information about the sex of the participants. Of these, exactly two-thirds of studies were conducted on men (Fig. 3). Methods: Fig. 3 also gives an overview of the methods used. The most popular is a tonometric approach, followed by blood gas analyzers (BGA), the mixing technique, continuous methods, and the Hemox Analyzer, all of which are briefly described in the "Discussion".

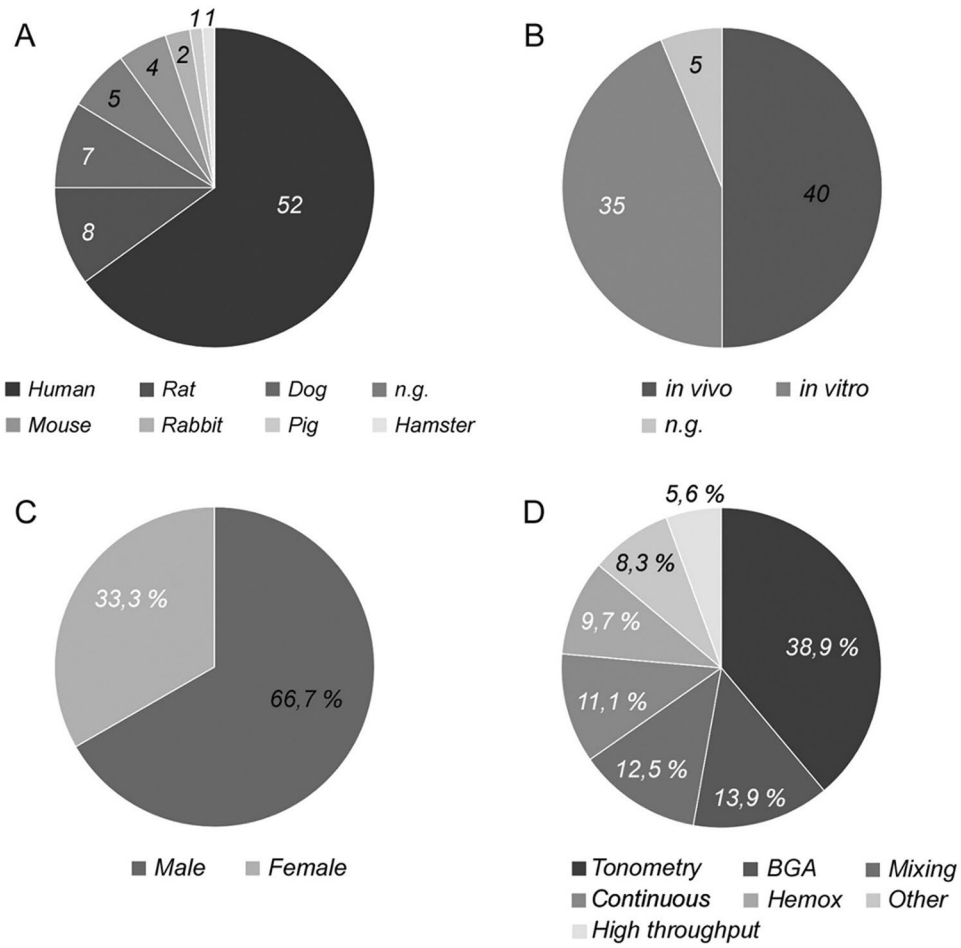

Fig. 3 Number of studies by test organisms (**A**), by test settings (**B**), and by the methods used to measure or calculate the ODC (**D**). **C** Percent distribution of studies between females and males

The results of the individual sources of evidence, grouped by area of specialization, are listed in Tables 2, 3, 4, and 5. All abbreviations used in these tables and further explanations of the entries can be found in the legend of Tables 2, 3, 4, and 5.

Discussion

Our search yielded less than a hundred studies on this topic. This is comparatively small considering the number of drugs in clinical use worldwide or in current development for clinical use. Thus, the vast majority of drugs routinely administered to humans have not been studied for their effects on Hb oxygen transport. In addition, we found that a significant proportion of the reviewed publications were of poor study quality, with many providing little or no information on statistics, number of subjects, methods, or even test organisms. Other studies suffer from small numbers of participants or test runs that are unlikely to produce statistically significant results. Unfortunately, many studies did not report the distribution of male and female participants, and when they did, males were overrepresented in most cases. This is a notable omission given that the P_{50} values are significantly different between women and men [13]. In addition, there is a remarkable proportion of studies in which the authors declared a conflict of interest (e.g., paid by the manufacturer of the product), which may also limit comparability of the results. Finally, a large number of studies are outdated and deal with substances that in some countries are no longer used or recommended in clinical use and have been replaced by others. This is the case, for example, for propranolol, a ß-blocker and class II antiarrhythmic used in cardiology with a significant rightward shift effect on the ODC shown in several studies. This effect is discussed to be due to the release of 2,3-BPG from the erythrocyte membrane and binding to Hb, thereby reducing the oxygen affinity of Hb [14]. This right-ward

Table 2 Results of individual sources of evidence, grouped into 12 specific disciplines (plus 1 "unclassified"). The order of publications within the disciplines is in vivo/human, in vivo/animal, in vitro human, and in vitro animal. Within these groups, the order is by year of publication (ascending). Abbreviations used: *Ad.*, administration; *C*, control group; *i.a.*, intraarterial; *i.c.*, intracutaneous; *i.m.*, intramuscular; *i.p.*, intraperitoneal; *i.v.*, intravenous; *n*, number of experiments; *n.g.*, not given; *n.s.s.*, not statistically significant; *p.o.*, per os; *qual.*, quality; *quant.*, quantity; *s.c.*, subcutaneous; *s.l.*, sublingual; *T*, test group. The percentage in column "Effect quant. (P_{50})" indicates the percentage change in the P_{50}. Numbers next to C or T refer to the number of individuals in the control and test group, respectively. "Own control" denotes the same individuals for test and control. *Opinion papers or reviews

Cardiology: Study/Journal	First Author	Year	Drug	Ad. Method/ in vivo/in vitro	blood sample	Human/ animal	n	Method	Effect qual./ Effect quant. (p50)	Statistical significance	Cohort Baseline p50
Oxygen affinity in red cells: changes induced in vivo by propranolol Science. 1972 Mar 24;175(4028):1372-3.	Oski	1972	Propranolol	n.g. in vivo/vitro	venous	Human	n.g.	n.g.	right shift + 8.7 %	p < 0,05	28,5 mmHg
The effect of aspirin on sickling and oxygen affinity of erythrocytes Proc Natl Acad Sci U S A. 1973 Dec;70(12):3707-10.	De Furia	1973	ASS	p.o. in vivo	venous	Human	C1/T8	Tonometric + BGA	n.s.s no effect	n.g.	26 mmHg
Altered hemoglobin-oxygen affinity with long-term propranolol therapy in patients with coronary artery disease Am J Cardiol. 1977 Jul;40(1):76-82.	Schrumpf	1977	Propranolol	p.o. in vivo	arterial/ venous	Human	12 (Own control)	Mixing Technique	right shift + 12.4 %	p < 0,01	28,2 mmHg
Nitroglycerin and blood oxygen dissociation curve of normal subjects. Am Heart J. 1979 Jun;97(6):815-6.	Clerbaux	1979	Nitroglycerine	s.l. in vivo	arterial	Human	T7	n.g.	n.s.s. n.g.	n.s.s.	26,7 mmHg
The haemoglobin-oxygen dissociation curve: in vivo and in vitro effects of five beta-adrenoceptor antagonists and lignocaine Br J Clin Pharmacol. 1981 Jan;11(1):19-24.	Trembath	1981	Propranolol, Practolol Atenolol, SL75212	i.v. in vivo	venous	Human	T5	Tonometric	n.s.s. n.g.	n.g.	26,0 mmHg
The effect of a single dose of propranolol on human erythrocytes in vivo. Eur J Clin Invest. 1981 Feb;11(1):65-8.	Reinhart	1981	Propranolol	p.o. in vivo	venous	Human	C6/T6	Tonometric	n.s.s. n.s.s.	p < 0,05	26,7 mmHg
Comparative evaluation of fifteen anti-sickling agents Blood. 1983 Apr;61(4):693-704.	Scatena	1995	Gemfibrozil	p.o. in vivo	n.g.	Human	n.g.	Tonometric	right shift + 15.1 %	p < 0,02	25,1 mmHg
Effect of propranolol and nitroglycerin on hemoglobin--oxygen affinity Eur J Pharmacol. 1976 Mar;36(1):267-71.	Gross	1976	Propranolol	i.c. in vivo	venous	Dog	T18	Tonometric + BGA	+ 6.1 % n.s.s.	p < 0,05	29.3 mmHg
The action of propranolol on factors concerned with the delivery of oxygen to the tissues Br J Pharmacol. 1981 Nov;74(3):643-9.	Ledingham	1981	Propranolol	p.o. in vivo	venous	Rat	n.g.	Mixing Technique	n.s.s. n.g.	n.s.s.	32 mmHg
Acetylation of sickle cell hemoglobin by aspirin Proc Natl Acad Sci U S A. 1973 May;70(5):1313-5	Klotz	1973	ASS	n.g. in vitro	venous	Human	n.g.	Tonometric + BGA	left shift - 33 %	n.g.	n.g.
Oxygen affinity and electrolyte distribution of human blood: changes induced by propranolol Science. 1973 Oct 19;182(4109):300-1.	Agostoni	1973	Propranolol	n.g. in vitro	venous	Human	n.g.	n.g.	right shift n.g.	n.g.	n.g.
The effect of macromolecular polyanions on the functional properties of human hemoglobin Eur J Biochem. 1977 Jun 15;76(2):339-43.	Amiconi	1977	Dextran Sulphate/Heparin	n.g. in vitro	venous	Human	n.g.	Tonometric	n.g. n.g.	n.g.	n.g.
Effects of some cardioactive drugs on the oxygen affinity of whole blood Acta Med Scand. 1979;205(1-2):49-52.	Berntorp	1979	Digoxin/Lasix Teofyllamin/CI-775	n.g. in vitro	venous	Human	C6/T6	BGA	n.s.s. n.g.	n.s.s.	27,1 mmHg
The effects of sodium nitroprusside and cyanide on haemoglobin function J Pharm Pharmacol. 1980 Apr;32(4):256-61.	Vesey	1980	Nitroprusside	n.g. in vitro	venous	Human	n.g.	Tonometric	left shift - 4 % / - 5 %	p < 0,01	26,8 mmHg 27,6 mmHg
Comparative evaluation of fifteen anti-sickling agents Blood. 1983 Apr;61(4):693-704.	Chang	1983	15 drugs	n.g. in vitro	venous	Human	n.g.	Continuous	n.g. n.g.	n.g.	n.g.
In vitro effects of pentoxifylline on hemoglobin affinity for oxygen and electrolytic equilibrium of human blood Ric Clin Lab. 1983 Oct-Dec;13(4):459-65.	Ferraresi	1983	Pentoxifylline	n.g. in vitro	venous	Human	n.g.	Tonometric	left shift n.g.	p < 0,05	n.g.
Analysis of the effect of bezafibrate on the oxygen dissociation curve of human hemoglobin FEBS Lett. 1984 Jun 11;171(2):187-91.	Wootton	1984	Bezafribrate	n.g. in vitro	venous	Human	n.g.	Hemox Analyzer	right shift n.g.	n.g.	n.g.
Sildenafil Increases the p50 and Shifts the Oxygen-Hemoglobin Dissociation Curve to the Right J Sex Med. 2015 Dec;12(12):2229-32.	Ellis	2015	Sildenafil	n.g. in vitro	venous	Human	T8 (own control)	Hemox Analyzer	right shift 4 % / 5 % / 7 % / 6 %	p < 0,05 for latter 3	24,12 mmHg
Effect of cilostazol on the p50 of the oxygen-hemoglobin dissociation curve. Int J Angiol. 2015 Mar;24(1):67-70.	McKoy	2015	Cilostazol	n.g. in vitro	n.g.	Human	T8 (own control)	Hemox Analyzer	right shift 5 % / 6,5 % / 12%	p < 0,01 for latter 2	28,27 mmHg
Aryloxyalkanoic Acids as Non-Covalent Modifiers of the Allosteric Properties of Hemoglobin Molecules. 2016 Aug 13;21(8):1057.	Omar	2016	Clofibrate	n.g. in vitro	venous	Human	n.g.	Tonometric	right shift + 5.2 %	n.g.	38,3 mmHg
Apixaban Interacts with Haemoglobin: Effects on Its Plasma Levels Thromb Haemost. 2018 Oct;118(10):1701-1712.	Sacco	2018	Apixaban	n.g. in vitro	venous	Human	n.g.	Tonometric	n.g. n.g.	n.g.	n.g.
Reaction of S-nitrosoglutathione with the heme group of deoxyhemoglobin J Biol Chem. 2000 Nov 24;275(47):36562-7.	Spencer	2020	S-Nitrosoglutathione	n.g. in vitro	n.g.	Human	n.g.	n.g.	n.g. n.g.	n.g.	n.g.
Resveratrol, a New Allosteric Effector of Hemoglobin, Enhances Oxygen Supply Efficiency and Improves Adaption to Acute Severe Hypoxia Molecules. 2023 Feb 22;28(5):2050.	Chu	2023	Resveratrol	n.g. in vitro	n.g.	Human/ Rat	n.g.	Oxygen Dissociation Assay	left shift n.g.	p < 0,05	n.g.
Oxygen affinity in stored canine blood: the effect of prednisolone Can J Comp Med. 1979 Apr;43(2):207-10.	Thompson	1979	Acid citrate dextrose	n.g. in vitro	venous	Dog	T6	Tonometric	right shift + 10 %	n.g.	15,3 mmHg
Nitric oxide effect on the hemoglobin-oxygen affinity. J Physiol Pharmacol. 2006 Mar;57(1):29-38.	Stepuro	2006	Nitric Oxide	n.g. in vitro	n.g.	Rabbit	C7/T7	Mixing Technique	left shift - 10 %	p < 0,05	35,43 mmHg

Table 3 Results of individual sources of evidence, grouped into 12 specific disciplines (plus 1 "unclassified"). The order of publications within the disciplines is in vivo/human, in vivo/animal, in vitro human, and in vitro animal. Within these groups, the order is by year of publication (ascending). Abbreviations used: *Ad.*, administration; *C*, control group; *i.a.*, intraarterial; *i.c.*, intracutaneous; *i.m.*, intramuscular; *i.p.*, intraperitoneal; *i.v.*, intravenous; *n*, number of experiments; *n.g.*, not given; *n.s.s.*, not statistically significant; *p.o.*, per os; *qual.*, quality; *quant.*, quantity; *s.c.*, subcutaneous; *s.l.*, sublingual; *T*, test group. The percentage in column "Effect quant. (P_{50})" indicates the percentage change in the P_{50}. Numbers next to C or T refer to the number of individuals in the control and test group, respectively. "Own control" denotes the same individuals for test and control. *Opinion papers or reviews

Anaesthesiology: Study/Journal	First Author	Year	Drug(s)	Ad. Method/ in vivo/in vitro	blood sample	Human/ Animal	n	Method	Effect qual./ Effect quant (p50)	Statistical significance	Cohort Baseline p50
Cardiovascular performance and oxyhemoglobin dissociation after acetazolamide in metabolic alkalosis Intensive Care Med. 1982;8(6):269-74.	Berthelsen	1982	Azetazolamide	i.v. in vivo	venous	Human	T12	BGA	n.s.s. n.s.s.	p > 0.05	26.6 mmHg
Effects of an antenatal load of pyridoxine (vitamin B6) on the blood oxygen affinity and prolactin levels in newborn infants and their mothers Acta Paediatr Scand. 1983 Jul;72(4):525-9.	Temesvari	1983	Pyridoxine (Vit. B6)	i.m. (12) / p.o. (12) in vivo	venous	Human (Antenatal)	C12/T24	Mixing Technique	right shift +18% (i.m.)/+9% (p.o.)	p < 0.001 p < 0.01	19,50 mmHg
Effect of nitrous oxide on the oxyhemoglobin dissociation curve and PO2 measurements. Anesthesiology. 1987 Feb;66(2):208-9.	Kambam	1987	Nitric Oxide	Inhalation in vivo	venous	Human	T20	Tonometric	right shift + 0.06 %	p < 0,001	26.8 mmHg
Effects of halothane, enflurane, and nitrous oxide on oxyhemoglobin affinity Anesthesiology. 1988 Apr;68(4):591-4.	Lanza	1988	Halothane, Enflurane, Nitrous Oxide	n.g. in vivo	venous	Human	T27	Tonometric	n.s.s./n.s.s. right shift n.s.s./n.s.s./+ 5.4%	p < 0,01	27.8/26.5/ 27.4 mmHg
Modulation of Hb-O2 affinity to improve hypoxemia in COVID-19 patients Clin Nutr. 2021 Jan;40(1):38-39. *	Woyke	2020	5-HMF	p.o. in vivo	n.g.	Human	n.g.	n.g.	left shift n.g.	n.g.	n.g.
The effect of morphine, meperidine, fentanyl and naloxone on the oxyhemoglobin dissociation curve. J Pharmacol Exp Ther. 1974 Jul;190(1):176-9.	Petty	1974	Morphine, Meperidine, Fentanyl, Naloxone	n.g. in vitro	venous	Human	T25 (own control)	Tonometric with BGA	n.g. n.g.	n.g.	n.g.
The effect of althesin (CT 1341) on the oxyhaemoglobin dissociation curve in vitro Br J Anaesth. 1976 Nov;48(11):1083-86.	Ishikawa	1976	Althesin	n.g. in vitro	venous	Human	C21/T21	Tonometric with BGA	right shift + 4 %	p < 0,005	29.05 mmHg
Covalent fixation of hemoglobin to dextran phosphates decreases its oxygen affinity Biochim Biophys Acta. 1990 Dec 5;1041(3):279-84.	Sacco	1990	Dextranes	n.g. in vitro	n.g.	Human	n.g.	Tonometric	n.g. n.g.	n.g.	n.g.
The impact of nebulized epoprostenol and iloprost on hemoglobin oxygen affinity: an ex vivo experiment Am J Physiol Lung Cell Mol Physiol. 2022 Jun 1;322(6):L898-L903.	Woyke	2022	Epoprostenol/Iloprost	n.g. in vitro	venous	Human	T20	High Throughput System	left shift / n.s.s. - 14 % / n.s.s.	p < 0.001 p < 0.17	26.3 mmHg
The effect of desflurane, isoflurane and sevoflurane on the hemoglobin oxygen dissociation curve in human blood samples Sci Rep. 2022 Aug 10;12(1):13633.	Ronzani	2022	Desflurane, Isoflurane, Sevoflurane	Inhalation in vitro	venous	Human	T22	High Throughput System	left shift/n.s.s./left shift - 3.3 % / n.s.s. / - 7.2 %	p = 0.005 p = 0.54 p < 0.001	27.9 mmHg
Effect of nitric oxide on the oxygen transport of human erythrocytes. J Toxicol Environ Health. 1977 May;2(5):1109-13.	Kon	2009	Nitric Oxide	n.g. in vitro	n.g.	n.g.	n.g.	Continuous	left shift n.g.	n.g.	n.g.
Nutrition Medicine:											
Long-term physiological effects of enhanced O2 release by inositol hexaphosphate-loaded erythrocytes. Proc Natl Acad Sci U S A. 1987 Oct;84(19):6894-8.	Teisseire	1987	Inositol Hexaphosphat	Transfusion in vivo	n.g.	Piglet	C1/T8	Dissociation Curve Analyzer	right shift + 45 %	p < 0.001	32,2 mmHg
The effect of fructose infusions on the oxygen transport system of human blood Eur J Clin Invest. 1976 Mar 31;6(2):121-5.	Standl	1976	Fructose	i.v. in vitro	arterial	Human	T9	n.g.	n.s.s. n.s.s.	n.g.	26,3 mmHg
Dose- and Sex-Dependent Changes in Hemoglobin Oxygen Affinity by the Micronutrient 5-Hydroxymethylfurfural and α-Ketoglutaric Acid Nutrients. 2021 Sep 29;13(10):3448.	Woyke	2021	5-HMF + alpha-Ketoglutaric acid	n.g. in vitro	venous	Human	n.g.	High Throughput System	left shift -4.8%/-21%/-69 %	p < 0.001	25,15 mmHg
Nephrology:											
Effects of phosphate loading on 2,3-diphosphoglycerate and maximal oxygen uptake Med Sci Sports Exerc. 1984 Jun;16(3):263-8.	Cade	1984	Sodium Phosphate	p.o. n.g.	n.g.	Human	T10 (own control)	n.g.	n.g. n.g.	n.g.	n.g.
Toxicology:											
Effects of chronic changes in hemoglobin-O2 affinity in rats. J Appl Physiol Respir Environ Exerc Physiol. 1979 Apr;46(4):816-22.	Teisseire	1979	Sodium Cyanate, o-iodosodium benzoate	i.p. in vivo	venous	Rat	T10/C20	Dissociation Curve Analyzer	left shift / right shift - 49 % / + 22 %	p < 0.001	35,2 mmHg
The hypoxic ventilatory response of rats with increased blood oxygen affinity. Respir Physiol. 1986 Nov;66(2):225-33.	Birchard	1986	Sodium Cyanate	i.p. in vivo	venous	Rat	n.g.	Mixing Technique	left shift - 34 %	p < 0.001	35,5 mmHg
Chronic administration of sodium cyanate decreases O2 extraction ratio in dogs J Appl Physiol (1985). 1988 Apr;64(4):1584-90.	Warley	1988	Sodium Cyanate	p.o. in vivo	venous	Dog	C8/T7	BGA	left shift - 32 %	p < 0.01	32,4 mmHg
Microvascular oxygen transport: impact of a left-shifted dissociation curve. Am J Physiol. 1992 Feb;262(2 Pt 2):H517-22.	Stein	1992	Sodium Cyanate	i.p. in vivo	arterial	Hamster	C7/T12	Biotonometric	left shift - 38 %	p < 0.05	26,1 mmHg

shift of the ODC might enhance oxygen extraction at the tissue level. However, propranolol has been replaced in many intensive care units for the treatment of arrhythmia by short acting ß-blockers like esmolol or landiolol, for which there are no data on potential effects on oxygen binding to Hb. This is another example of why further studies in this area are urgently needed.

There may be many reasons for this unsatisfying study situation. We speculate that the limited accessibility of appropriate analytical methods necessary to perform an ODC measurement is one of them. For example, the Hemox Analyzer is only available in a few institutions because it is quite expensive for a single-purpose device. Other methods or devices (except blood gas analysis) are not commercially available and would have to be custom-built, which could prevent many researchers from carrying out specific projects. In addition, the vast majority of methods suffer from the limitation that measurements in single cuvette systems, such as the Hemox Analyzer, are cumbersome, time-consuming, and do not provide the ability to run controls side by side. Another reason for the paucity of studies may be that the interest in the ODC has steadily declined since the 1970s and 1980s, as analyzed in Fig. 2. We can only speculate, but perhaps the impact of the ODC in a clinical setting has been overlooked, or people are not really aware of its significance.

The importance of the ODC has already been mentioned in the introduction but should be underscored by the following examples: The working myocardium has an exceptionally high oxygen extraction rate and is very vulnerable in ischemic and hypoxic situations. Right- or left-ward shifted ODCs, resulting in either increased (right-ward shifted) or decreased (left-ward shifted) tissue oxygenation, would have a significant impact on heart functionality, especially in any kind of diseased state when oxygen delivery is generally low. For example, Lucas et al. injected 5-hydroxymethylfurfural (5-HMF) or only vehicle to hamsters [15]. The 5-HMF induced left-ward shift of the ODC resulted in improved cardiac indices, stroke volume, cardiac output, ejection fraction, and stroke work compared to control group when exposed to hypoxia. On the other hand, Watanabe and colleagues showed that mice with severe heart failure and treated with the oxygen affinity modulator RSR13 (which induces a right-ward shift) had improved treadmill running performance due to increased oxygen delivery in skeletal muscle [16]. P_{50}

Table 4 Results of individual sources of evidence, grouped into 12 specific disciplines (plus 1 "unclassified"). The order of publications within the disciplines is in vivo/human, in vivo/animal, in vitro human, and in vitro animal. Within these groups, the order is by year of publication (ascending). Abbreviations used: *Ad.*, administration; *C*, control group; *i.a.*, intraarterial; *i.c.*, intracutaneous; *i.m.*, intramuscular; *i.p.*, intraperitoneal; *i.v.*, intravenous; *n*, number of experiments; *n.g.*, not given; *n.s.s.*, not statistically significant; *p.o.*, per os; *qual.*, quality; *quant.*, quantity; *s.c.*, subcutaneous; *s.l.*, sublingual; *T*, test group. The percentage in column "Effect quant. (P_{50})" indicates the percentage change in the P_{50}. Numbers next to C or T refer to the number of individuals in the control and test group, respectively. "Own control" denotes the same individuals for test and control. *Opinion papers or reviews

Oncology: Study/Journal	First Author	Year	Drug(s)	Ad. Method/ in vivo/in vitro	blood sample	Human/ animal	n	Method	Effect qual./ Effect quant (p50)	Statistical significance	Cohort Baseline p50
Allosteric modification of oxygen delivery by hemoglobin. Anesth Analg. 2001 Mar;92(3):615-20.	Wahr	2001	RSR13	i.v. in vivo	n.g.	Human	C2/T5	Tonometric	right shift n.g.	n.g.	n.g.
Enhanced oxygenation in vivo by allosteric inhibitors of hemoglobin saturation. Am J Physiol. 1993 Oct;265(4 Pt 2):H1450-3.	Khandelwal	1993	RSR4, RSR13	i.p. in vivo	venous	Mouse	T5, T4	Hem-O-Scan	right shift + 25 % / + 53 %	p < 0,001 p < 0,004	40 / 41 mmHg
31P MRS to monitor the induction of tumor hypoxia by the modification of the oxygen affinity of hemoglobin using BW 589C. Int J Radiat Oncol Biol Phys. 1994 May 15;29(2):285-8.	Kalra	1994	BW 589C	p.o. in vivo	venous	Mouse	T5	n.g.	left shift n.g.	n.g.	n.g.
Effects of FI(O(2)) on hemodynamic responses and O(2) transport during RSR13-induced reduction in P(50). Am J Physiol. 1999 Jul;277(1):H290-8.	Eichelbrönner	1999	RSR13	i.p. in vivo	venous	Rat	T14	BGA	right shift + 28 %	p < 0,05	36,7 mmHg
Effects of a pharmacologically-induced shift of hemoglobin-oxygen dissociation on myocardial energetics during ischemia in patients with coronary artery disease. J Cardiovasc Magn Reson. 2005;7(4):657-66.	Najjart	2009	RSR13	i.v. in vivo	n.g.	Dog	T7	Tonometric	right shift + 25 %	p < 0,01	26,7 mmHg
The secondary alcohol and aglycone metabolites of doxorubicin alter metabolism of human erythrocytes Braz J Med Biol Res. 2003 Dec;36(12):1643-51.	Misiti	2003	Doxorubicin	n.g. in vitro	venous	Human	n.g.	Tonometric	left shift - 22 %	p < 0.05	n.g.
The impact of cannabinoids on methemoglobin formation and hemoglobin oxygen affinity: An ex-vivo study Toxicol. 2024 June;505:153832	Frisch	2024	Cannabinoids	n.g. in vitro	venous	Human	C11/T11	High Throughput System	right shift + 4,6 %	n.s.s.	25,6(m)/28,5(f)
RSR13, a synthetic modifier of hemoglobin-oxygen affinity, enhances the recovery of stunned myocardium in anesthetized dogs J Pharmacol Exp Ther. 1998 Apr;285(1):1-8.	Pagel	1998	RSR13	n.g. n.g.	arterial	Dog	n.g.	Tonometric	right shift + 40 %	n.g.	n.g.
Immunology:											
The binding of ciamexone to globin: its demonstration and some accompanying effects in rats Toxicol Appl Pharmacol. 1987 Mar 15;87(3):490-7.	Isert	1987	Ciamexone	p.o. in vivo	venous	Rat	T3	Tonometric	n.s.s. n.s.s.	p < 0,05	37,3 mmHg
Analysis of the relationship between hemoglobin-oxygen affinity and lipid peroxidation during fever Acta Biochim Pol. 1995;42(1):69-74	Borisiuk	1994	Pyrogenal	i.v. in vivo	venous	Rabbit	n.g.	Mixing Technique	right shift + 13 %	p < 0,05	29,8 mmHg
The effect of methylprednisolone sodium succinate on erythrocyte and haemoglobin function Clin Sci (Lond). 1980 Sep;59(3):163-8.	Brada	1980	Methylprednisolon	n.g. in vitro	venous	Human	n.g.	Tonometric	right shift + 13.08 %	n.g.	n.g.
Endocrinology:											
Effects of androgens on oxygen affinity in vivo and 2,3-diphosphoglycerate content of red cells in peripheral arterial insufficiency Scand J Clin Lab Invest. 1976 Dec;36(8):801-4.	Bille-Brahe	1976	Testosteron	i.m. in vivo	venous	Human	C6/T6	Radiometer	n.s.s. n.s.s.	n.s.s.	n.g.
An adverse effect of insulin on the oxygen-release capacity of red blood cells in nonacidotic diabetics Metabolism. 1978 Aug;27(8):927-34.	Ditzel	1978	Insulin	n.g. in vivo	arterial	Human	C15/T10	Continuous	right shift + 2 %	p < 0,001	26,6 mmHg
Androgen therapy in hemodialysis patients: I. Effects on red cell oxygen transport Kidney Int. 1987 Jan;31(1):100-6.	Hendler	1987	Var. Androgens	i.m. in vivo	venous	Human	C15/T32	Hem-O-Scan	n.s.s. n.s.s.	n.s.s.	27,9 mmHg
The effects of 2,3-diphosphoglycerate, adenosine triphosphate, and glycosylated hemoglobin on the hemoglobin-oxygen affinity of diabetic patients Braz J Med Biol Res. 2003 Jun;36(6):731-7.	Castilho	2003	Insulin	n.g. in vivo	venous	Human	C19/T41	Mixing Technique	n.s.s. n.s.s.	n.s.s.	26,8 mmHg
Effect of Hyperoxia and Androgen on Red Cell 2,3-Diphosphoglycerate and Oxygen Affinity Acta Haematol. 1976;55(5-2):306-12.	Gorshein	1976	19-Nortestosteron Decanoat	n.g. in vivo	n.g.	Mouse	n.g.	n.g.	right shift + 5 %	p < 0,05	40,5 mmHg
Sodium o-iodobenzoate and hemoglobin-oxygen affinity: in vivo effects. J Appl Physiol. 1976 Dec;41(6):900-4.	Litwin	1976	ortho-iodo sodium benzoate	n.g. in vivo	venous	Dog	T7 (Own control)	Continuous	right shift + 17 %	n.g.	26,8 mmHg
Effect of ortho-Iodo sodium benzoate on hemoglobin-oxygen affinity in normal and ischemic myocardium. J Pharmacol Exp Ther. 1977 Oct;203(1):72-81.	Gross	1977	ortho-iodo sodium benzoate	n.g. in vivo	venous	Dog	T10	Tonometric	n.g. +7 %/+13%/+24%	p < 0,001	31,2 mmHg
Oxygen affinity of hemoglobin and peripheral nerve degeneration in experimental diabetes J Neurol Sci. 1991 Feb;101(2):204-7.	Farber	1991	Insulin	i.v. in vivo	venous	Rat	C10/T10	n.g.	left shift n.g.	n.g.	n.g.
Effect of melatonin on the blood oxygen transport during hypothermia and rewarming in rats Adv Med Sci. 2008;53(2):234-9.	Hlutkin	2008	Melatonin	i.p. in vivo	n.g.	Rat	T48	Mixing Technique	right shift n.s.s./+ 7.3%/+9.6%	p < 0,05	30,1 mmHg
Thyroid hormones and the oxygen affinity of hemoglobin Ann Intern Med. 1971 Apr;74(4):632-3 *	Schussler	1971	Thyroid hormones	n.g. in vitro	n.g.	Human	n.g.	n.g.	right shift n.g.	n.g.	n.g.

was increased by 12.5% in their experiments. In humans, a right-ward shift of the ODC by the same amount would increase P_{50} from a normal value of 26.7 (Fig. 4; black line) to 30.0 mmHg (dashed line). Assuming normoxia and normal pulmonary oxygenation, Hb is almost completely saturated in both cases (SO_2 97.3% vs. SO_2 96.3%; right vertical solid line), while at the tissue level, assuming a PO_2 of 20 mmHg (left vertical solid line), SO_2 is lower in the right-shifted ODC and correspondingly more O_2 is extracted (SO_2 31.4% vs. SO_2 25%). In this example, the oxygen extraction rate ($O_2ER = (SaO_2—SvO_2) / SaO_2$); a = arterial, v = venous) is 74.0% compared to 67.7%. Further assuming a Hb concentration of 150 g/l and using a Hüfner number of 1.34 ml O_2/g Hb, this would mean that for every liter of cardiac perfusion, an additional ~ 11 ml of pure O_2 would be available to the cells. Although we are not aware of a human cohort study demonstrating a direct physiological effect on patients with this additional amount of O_2, all cardiologists would probably agree that anything that improves tissue oxygenation and prevents tissue hypoxia should be beneficial to a critically ill patient at some point. In a case report by Al-Qudsi et al., two patients with persistent severe hypoxic respiratory failure were treated with the anti-sickling agent voxelotor [17]. This drug stabilizes Hb in its oxygenated state by inducing a left-ward shift of the ODC. During the treatment, the oxygen saturation to FiO_2 ratio increased substantially, reducing the invasiveness of mechanical ventilation. Unfortunately, the change in tissue oxygenation by this left-shifted ODC was not investigated in this study.

Our search revealed a handful of methods for recording an ODC, and the most common ones are briefly described here. First and foremost is a tonometric approach, where blood samples are successively exposed to ≥ 2 different gas mixtures with predefined PO_2, while SO_2 is determined by dual wavelength absorption measurements. Continuous

Table 5 Results of individual sources of evidence, grouped into 12 specific disciplines (plus 1 "unclassified"). The order of publications within the disciplines is in vivo/human, in vivo/animal, in vitro human, and in vitro animal. Within these groups, the order is by year of publication (ascending). Abbreviations used: *Ad.*, administration; *C*, control group; *i.a.*, intraarterial; *i.c.*, intracutaneous; *i.m.*, intramuscular; *i.p.*, intraperitoneal; *i.v.*, intravenous; *n*, number of experiments; *n.g.*, not given; *n.s.s.*, not statistically significant; *p.o.*, per os; *qual.*, quality; *quant.*, quantity; *s.c.*, subcutaneous; *s.l.*, sublingual; *T*, test group. The percentage in column "Effect quant. (P_{50})" indicates the percentage change in the P_{50}. Numbers next to C or T refer to the number of individuals in the control and test group, respectively. "Own control" denotes the same individuals for test and control. *Opinion papers or reviews

Psychiatry: Study/Journal	First Author	Year	Drug(s)	Ad. Method/ in vivo/in vitro	blood sample	Human/ animal	n	Method	Effect qual./ Effect quant (p50)	Statistical significance	Cohort Baseline p50
Stabilization of the T-state of ferrous human adult haemoglobin by chlorpromazine and trifluoperazine Biotechnol Appl Biochem. 1999 Oct;30(2):185-7.	Ascenzi	1999	Chlorpromazin, Trifluoperazine	n.g. n.g.	n.g.	n.g.	n.g.	n.g.	n.g. n.g.	n.g.	n.g.
Radiology:											
Depression of intramyocardial oxyhemoglobin dissociation by angiographic contrast media. Am Heart J. 1980 Feb;99(2):193-7.	Sheps	1980	Renografin 76	i.v. in vivo	arterial	Human	T11	Continuous	left shift - 10 %	p < 0.05	27.3 mmHg
Contrast Media Adversely Affect Oxyhemoglobin Dissociation Anesth Analg. 1990 Jul;71(1):73-6.	Kim	1990	Isovue-370	i.a. in vivo	arterial	Human	T10	Tonometric	left shift - 30 %	p < 0.05	25.3 mmHg
Phytomedicine:											
Phthalide Derivatives from Angelica Sinensis Decrease Hemoglobin Oxygen Affinity: A New Allosteric-Modulating Mechanism and Potential Use as 2,3-BPG Functional Substitutes Sci Rep. 2017 Jul 14;7(1):5504.	Chen	2017	Angelica Sinensis	n.g. in vitro	n.g.	Human	n.g.	Hemox Analyzer	right shift n.g.	n.g.	n.g.
Hematology:											
Erythropoetin treatment can increase 2,3-diphosphoglycerate levels in red blood cells. Scand J Clin Lab Invest. 2001;61(5):337-40.	Sandhagen	2001	Erythropoetin	s.c. in vivo	n.g.	Human	C5/T8	BGA	n.s.s. n.g.	n.g.	n.g.
Increased hemoglobin-oxygen affinity ameliorates bleomycin-induced hypoxemia and pulmonary fibrosis Physiol Rep. 2016 Sep;4(17):e12965.	Geng	2016	GBT1118	p.o. in vivo	arterial	Mouse	C12/T36	Hemox Analyzer	left shift n.g.	p < 0.01	n.g.
Mechanisms Underlying the Effects of Chloroquine on Red Blood Cells Metabolism Int. J. Mol. Sci. 2024, 25(12), 6424.	Russo	2024	Chloroquine	in vitro	venous	Human	n.g.	Tonometric	left shift n.g.	n.g.	n.g.
Unclassified:											
Intravenous infusion of inosine in man: effect on erythrocyte 2,3-diphosphoglycerate concentration and on blood oxygen affinity Scand J Clin Lab Invest. 1973 Nov;32(3):205-10.	DeVerdier	1973	Inosine	i.v. in vivo	venous	Human	T2	Continuous	n.s.s. n.s.s.	n.g.	n.g.
Effect of the diphosphonate ethane-l-hydroxy-l, l-diphosphonate (EHDP) on hemoglobin oxygen affinity of diabetic and healthy subjects Microvasc Res. 1977 May;13(3):355-61.	Ditzel	1977	EHDP	p.o. in vivo	venous	Human	C5/T14	Continuous	right shift + 4,3 %	p < 0.025	27,4 mmHg
Effect of iodoacetate and fluoride on the position of the haemoglobin oxygen dissociation curve of human whole blood Nature. 1968 Aug 31;219(5157):936-8.	Engel	1968	Iodacetate, Fluorid	n.g. in vitro	venous	Human	n.g.	Mixing technique	left shift / left shift - 50 % / -4 %	n.g.	29,7 mmHg
Acylation of hemoglobin by glutarylsalicylamide and its effect on oxygen transport properties Hemoglobin. 1978;2(2):101-16.	Tam	1978	Glutarylsalicylamide	n.g. in vitro	venous	Human	n.g.	Tonometric	right shift + 60,7%	n.g.	n.g.
A quantitative analysis of the effects of 2,3-diphosphoglycerate, adenosine triphosphate and inositol hexaphosphate on the oxygen dissociation curve of human haemoglobin J Physiol. 1978 Oct;283:397-407.	Goodford	1978	ATP, Insoitol Hexaphosphate	n.g. in vitro	venous	Human	n.g.	Tonometric	right shift / right shift n.g.	n.g.	n.g.
LR16, a compound with potent effects on the oxygen affinity of hemoglobin, on blood cholesterol, and on low density lipoprotein Proc Natl Acad Sci U S A. 1988 Aug;85(16):6117-21.	Lalezari	1988	LR16	n.g. in vitro	venous	Human	T2	Hemox Analyzer	right shift + 95 %	n.g.	20 mmHg
Reestimation of the effects of inorganic phosphates on the equilibrium between oxygen and hemoglobin. Intensive Care Med. 1992;18(4):222-5.	Clerbaux	1992	Inorganic Phosphates (K_2HPO_4)	i.v. in vitro	venous	Human	C10/T10	Continuous	right shift + 17.3 %	p < 0.001	25,5 mmHg
Chemical manipulations of tissue oxygenation for therapeutic benefit Int J Radiat Oncol Biol Phys. 1989 May;16(5):1125-30. *	Guichard	1989	n.g.	n.g. n.g.	n.g.	n.g.	n.g.	n.g.	n.g. n.g.	n.g.	n.g.

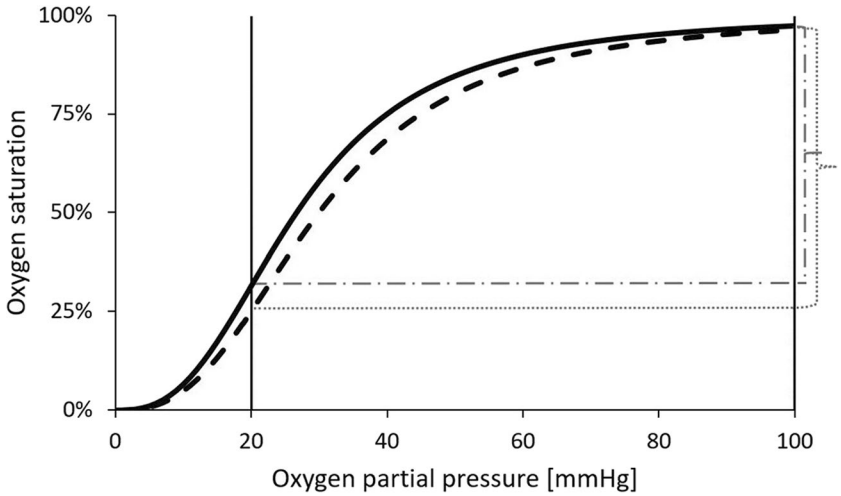

Fig. 4 Standard ODC (black sigmoidal curve) and ODC with a 12.5% increase in P_{50} (dashed curve). Given a tissue PO_2 of 20 mm Hg (left vertical line), O_2 extraction (curly brackets) is greater in the right-shifted ODC. For details, see Text

methods, in which the oxygen content of the gas phase is constantly decreasing or increasing, require the measurement of PO_2 and SO_2 in the sample at certain time intervals. Continuous methods are largely based on the method described by Duvelleroy and colleagues, where a known volume of deoxygenated blood is exposed to a known volume of O_2 and PO_2 and oxygen content are measured [18]. In the mixing technique, blood samples are divided into two aliquots, one exposed to an oxygen-rich gas mixture ($SO_2 = 100\%$) and the other to an oxygen-free gas ($= SO_2$ 0%). These two aliquots are then mixed in predefined volume fractions to obtain aliquots of known SO_2.

PO_2 is then measured in these aliquots. In vivo studies are usually based on blood gas analysis, where PO_2 and SO_2 are measured from a blood sample and the P_{50} is then extrapolated based on a predefined algorithm [19]. Finally, the Hemox Analyzer is a commercially available instrument (TCS Scientific Corp., PA, USA) that has been on the market for more than 40 years. It determines the ODC by exposing 2–50 µl of whole blood or hemolysate, diluted in 5 ml of buffered, anti-foaming solution, to a decreasing partial pressure of oxygen in an optical cuvette under constant agitation. The change in oxygen tension is detected by a Clark oxygen electrode inside the cuvette, while the decrease in oxyhemoglobin fraction (% HbO_2) is simultaneously monitored by dual wavelength spectroscopy at 560 nm and 576 nm, respectively. Recently, high-throughput assays have been developed that allow simultaneous measurements of large numbers of samples in microplate reader instruments [20, 21].

Our search has limitations that should be addressed here: First, our scoping review may not be fully replicable by all researchers, as it was limited to publications accessible through our institutional subscriptions. This limitation is important, as different institutions have varying agreements with publishers, and these agreements change over time (see Supplementary Information for the full list of journals accessible through our library). Second, our review does not claim to be exhaustive. Each search mask returns results based on its specific criteria, meaning that papers without the defined keywords may be missed. To avoid this, one would need to define more search forms, which, however, would significantly increase the effort while simultaneously reduce reproducibility. We opted for a strategy we believed would yield the most comprehensive results. Next, we consulted only two electronic databases, PubMed and the Cochrane Library, recognizing that other databases and libraries may include additional studies relevant to this work. However, PubMed was chosen because it is the most popular and likely most relevant database, with 23 million references in 2014 [22]. The Cochrane Library, with 800,000 references in 2014 [22], provides high-quality, peer-reviewed evidence in medical research and other services, mostly in the form of reviews. Google Scholar was not included because it returned almost identical results to PubMed. Furthermore, most of the studies are quite old. More than half of them were published before 1990, and most of them date back to the 1970s. Also, there were also almost no studies from the 1960s and earlier. There could be several reasons for this: English as a scientific language may not have been so common, the databases have not yet fully captured older or very old papers electronically, or the publications are not available in full text (only abstracts), so they did not meet our selection criteria. Another reason could be that the Hemox Analyzer, which greatly simplified the often complex measurements, was not introduced before the 1980s.

Conclusions

The search yielded a manageable number of studies with statistically significant effects of dozens of drugs on the ODC. In most cases, these effects were a right-ward shift, which would result in improved tissue oxygenation. This information may be relevant to conditions such as pulmonary diffusion disorders, peripheral vascular diseases, or coronary artery diseases. However, the research is incomplete and highly fragmented, and awareness of the therapeutic implications is still marginal.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00228-024-03781-8.

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Author contribution All authors contributed to the study conception. Data collection and analysis was performed by L.L., selection of relevant papers was performed by all authors, manuscript was written by T.H. and S.W..

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

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