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Review

Systematic Review and Meta-Analysis of the Impact of Hypoxia on Infarcted Myocardium: Better or Worse?

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Key Words
myocardial infarction • hypoxemia • hypoxia • hemodynamic • meta-analysis

Abstract
Background/Aims: Patients with myocardial infarction and hypoxemia require supplemental oxygen. However, the current therapeutic paradigm is contradicted by several recent studies in which the post-infarcted heart appears to benefit from systemic hypoxia. With this systematic review and meta-analysis, we aimed to discover whether systemic hypoxia is beneficial or detrimental to the infarcted myocardium. ***Methods:*** We conducted an electronic search of the PubMed, EMBASE, and Web of Science databases and extracted the outcomes of cardiac function, geometry, and hemodynamics. A random-effect model was applied when the I^2 value of greater than 50%. The sensitivity analysis was performed by omitting one study at a time, and publication bias was assessed using Egger's test. In addition, the quality of studies was evaluated using the risk of bias tool devised by the Systematic Review Centre for Laboratory Animal Experimentation. ***Results:*** Six reports comprising 14 experiments were ultimately screened from among 10,323 initially identified preclinical studies. Few studies reported the method of randomization and none described allocation concealment, random outcome assessment or blinding. Overall, chronic hypoxia was found to have a beneficial effect on the ejection fraction (standard mean difference [SMD] = 5.39; 95% confidence interval [CI], 3.83 to 6.95; $P < 0.001$) of the infarcted heart, whereas acute hypoxia significantly improved hemodynamics, as indicated by an increase in the maximal rate of rise of left ventricular pressure (SMD = 1.27; 95% CI, 0.27 to 2.28; $P = 0.013$) and cardiac output (SMD = 1.26; 95% CI, 0.34 to 2.18; $P = 0.007$) and a decrease in total systematic vascular resistance (SMD = −0.89; 95% CI, −1.24 to −0.53; $P < 0.001$). Furthermore, a reduced oxygen content increased the stroke volume ($P = 0.010$). However, hypoxia reduced the end-systolic (SMD = −2.67; 95% CI, −4.09 to −1.26; $P < 0.001$) and end-diastolic (SMD = −3.61; 95% CI, −4.65 to −2.57; $P < 0.001$) left ventricular diameters and increased the total pulmonary resistance (SMD = 0.76; 95% CI,

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0.20 to 1.33; *P* = 0.008), pulmonary arterial mean pressure (SMD = 2.02; 95% CI, 0.23 to 3.81; *P* = 0.027), and left atrial pressure (SMD = 1.20; 95% CI, 0.57 to 1.82; *P* < 0.001). ***Conclusion:*** Hypoxia significantly improved heart function after infarction, with particular beneficial effects on systolic function and hemodynamics. However, it had slightly adverse effects on pulmonary circulation and left ventricular geometry. A lower inspired oxygen concentration may improve cardiac function, although further research is needed to determine the optimum level of hypoxia. Finally, more studies of hypoxia and myocardial infarction in larger species are required before these findings can be incorporated into therapeutic guidelines.

Introduction

Myocardial infarction (MI) is among the most common cardiovascular diseases worldwide and causes more than 370, 000 deaths each year in the United States [1]. At a basic pathophysiological level, MI induces hypoxemia in 32% to 70% of patients who do not receive oxygen therapy [2, 3] and 5% to 27% of those who do receive oxygen therapy [3, 4]. Accordingly, the latest American Heart Association guideline for ST-elevation MI (STEMI) [5] requires supplemental oxygen administration for MI patients with hypoxemia. However, the Air Versus Oxygen in ST-Elevation Myocardial Infarction (AVOID) trial indicated potential adverse physiological effects of supplemental oxygen in nonhypoxic patients with MI [6].

Although some investigators have suggested that inducible systemic hypoxia may facilitate recovery of the infarcted myocardium [7, 8], hypoxia is generally thought to aggravate hypoxemia [9]; in turn, hypoxemia is known to induce more severe cardiac dysfunction after MI [10]. Accordingly, it remains unclear whether hypoxia beneficial or detrimental to patients with MI. Given the prevalence and lethality of MI, this problem must be resolved quickly to improve therapeutic strategies for MI. Accordingly, this systematic review and meta-analysis aimed to compare the effects of systemic hypoxia and room air on cardiac function in previously published animal models of MI.

Materials and Methods

This systematic meta-analysis was performed according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Fig. S1 - For all supplemental material see www.karger.com/10.1159/000495397) [11, 12].

Search Strategy

To identify the effects of hypoxia in animal models, a systematic search of the PubMed, EMBASE, and Web of Science databases was conducted through June 27, 2017. The following search terms were used: “Myocardial Infarction” [MeSH Terms] OR “Myocardial Infarction” [All Fields] AND (“Hypoxia” [MeSH Terms] OR “Hypoxia” [All Fields]. References from the related reviews and articles were then scrutinized to identify other potentially relevant studies.

Study selection

All controlled studies of hypoxia treatment in an animal model of MI were eligible for inclusion. No language or species limitations were imposed on the selection. Included studies were those that applied systematic hypoxia with or without low atmospheric pressure and presented data related to cardiac function, such as ejection fraction (EF), cardiac output or heart rate. If data were reported more than once, only the study with the most recent data was included. Two authors (Bo Pang and Fei Zhao) independently screened the search results for potential inclusion. All disputes were resolved by consensus.

Data extraction and quality assessment

Data were extracted independently by two reviewers (Yang Zhou and Bin He) using a standard electronic sheet and were cross-checked to reach a consensus. Graphical data were extracted using GetData Graph Digitizer v2.25 software (GetData Pty Ltd., New South Wales, Australia). Extracted details of the studies and animal models included the name of the first author, year of publication, country, cases/controls, animal variety, age, sex, weight, housing conditions, degree of hypoxia (oxygen content, duration, and pressure), intervention protocol, hypoxemia parameters (arterial partial pressures of oxygen, oxygen saturation, arterial partial pressures of carbon dioxide, and pH), cardiac function parameters (EF, hemodynamics, or heart rate) and average fibrosis area. For all outcomes, the number in each group and the method of assessment were also recorded.

Two investigators (Wei Huang and Fan Zhang) independently conducted a methodological quality assessment of all selected studies. All eligible studies were assessed using the risk of bias tool devised by the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) [13], which addresses the following five domains: selection bias, performance bias, detection bias, attrition bias, and reporting bias. Disagreements regarding quality assessment were resolved by discussion.

Statistical analysis

All data were combined and analyzed using STATA version 14.0 (Stata Corporation, College Station, TX). Continuous data from studies using different methods and units were expressed as standard mean differences (SMDs) and 95% confidence intervals (CIs), and data from studies using the same method and units were expressed as weighted mean differences (WMDs). If baseline data were available, the difference between the baseline and end-point was determined to assess the effect of hypoxia; end-point data were used alone if baseline data were not available. A random-effect model was applied to obtain a conservative estimate that considered both within-study and between-studies variability [14]. Heterogeneity was evaluated using the I^2 statistic at a significance level of less than 0.10 [14]; here, an I^2 value of greater than 50% was considered to indicate a high degree of heterogeneity [15, 16]. A sensitivity analysis was performed by omitting one study at a time. Publication bias was assessed using Egger's test [17]. If publication bias was overt, a trim-and-fill method was used to pool an adjusted relative risk (RR) that included potential missing studies [18]. An analytical result was considered statistically significant if the two-sided *P* value was less than 0.05.

Results

Study characteristics

We retrieved a total of 10, 303 published studies from the PubMed, EMBASE, and Web of Science databases and an additional 20 through a search of reference lists (Fig. 1). Of these, 688 were deemed eligible for full-text review after the title and abstract review. Eighteen controlled studies were identified from full texts, six of which reported 14 experiments that met the inclusion criteria for the meta-analysis [7, 8, 19-22]. These articles included one letter, one short communication, and four full articles. One article described a mouse model of MI [7], one described a rat model [8], and four described a canine model [19-22]. Two studies of systematic hypoxia had been conducted for 1 to 3 weeks, and four studies had used transient hypoxia for 3 to 15 minutes. All studies used continuous normobaric hypoxia, in which oxygen is replaced with nitrogen. The four canine studies applied inspired hypoxic gas, whereas the rat and mouse studies used hypoxic cabinets. These methods are considered equivalent because both allow the animal to inspire the hypoxic gas. All measurements were detected at the end of the period of hypoxia. The characteristics of the selected studies are summarized in Table 1.

Study quality

Each of the included studies was determined to have a low risk of bias (Table 2). All six studies reported baseline characteristics. Although all six studies also reported whole studies, only one clearly presented the method of randomized sequence generation and the process of random housing. No study discussed allocation concealment, random outcome assessment, or the blinding of caregivers, researchers, and outcome assessors. Four studies mentioned reporting bias, and the other four reported attrition bias.

Improvement in cardiac function

In one study that reported two animal experiments, chronic hypoxia enhanced the EF (SMD = 5.39; 95% CI, 3.83 to 6.95; $P < 0.001$) but did not significantly increase fractional shortening (SMD = 0.14; 95% CI, −1.20 to 1.48; $P = 0.839$). Five studies including two rat and 10 dog experiments demonstrated a reduced heart rate under chronic hypoxia (SMD = −1.42; 95% CI, −2.13 to −0.72; $P < 0.001$) but no significant changes under acute hypoxia (SMD = −0.27; 95% CI, −0.55 to 0.01; $P = 0.058$; Fig. 2). A subgroup analysis stratified by oxygen concentration revealed that none of the concentrations mentioned in the included studies had a significant effect on the heart rate ($P = 0.546$; Fig. 3).

Improvement in cardiac geometry under chronic hypoxia

Chronic hypoxia significantly reduced the end-systolic left ventricular diameter (LVDs) (SMD = −2.67; 95% CI, −4.09 to −1.26; $P < 0.001$) and end-diastolic left ventricular diameter (LVDd) (SMD = −3.61; 95% CI, −4.65 to −2.57; $P < 0.001$; Fig. 4). However, no significant geometrical changes were observed in the end-systolic posterior wall thickness ($P = 0.071$), end-diastolic posterior wall thickness ($P = 1.000$), end-systolic anterior wall thickness ($P = 0.852$), or end-diastolic anterior wall thickness ($P = 0.455$; Table 3).

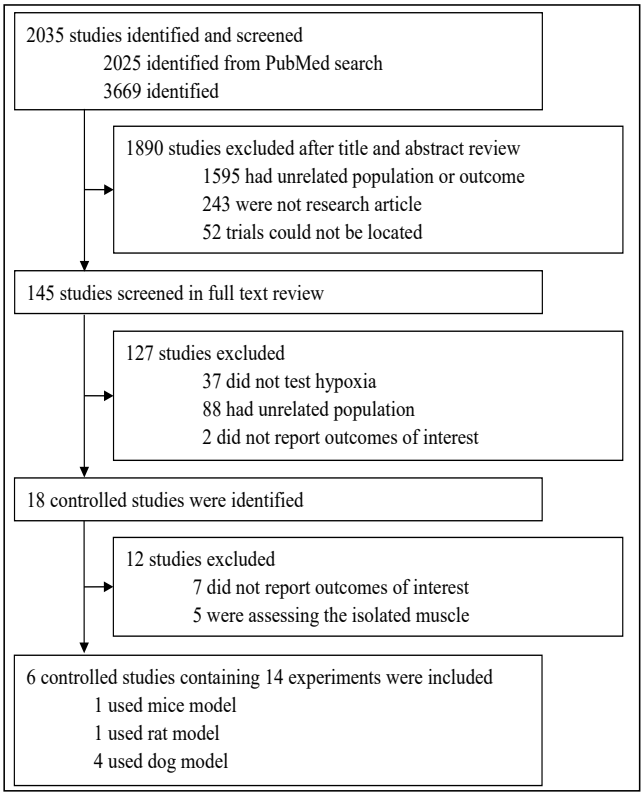

Fig. 1. Study selection procedure. A systematic database search yielded 10,323 published studies. After screening the titles/abstracts and full texts, six studies were deemed eligible for inclusion in the meta-analysis.

Table 1. Characteristics of Studies Included in the Meta-analysis. m, month; w, week; min, minute; n.a., not available

Author	Year	Publication Type	Country	Species	Age	Body Weight	Environment	Oxygen Concentration	Duration of Hypoxia
Nakada Y, et al. (a)[7]	2017	Letter	USA	C57BL/6J mice	2 m	n.a.	equivalent amount of food in	7%	2 w
Nakada Y, et al. (b)[7]					3 m	n.a.	both group	7%	3 w
Hrdlicka J, et al.(a)[8]	2016	Short communication	Czech Republic	Male Wistar rats	2.5 m	340–390 g	23°C; 12:12-h lightdark cycle, water and standard chow diet ad libitum	12%	1 w
Hrdlicka J, et al.(b)[8]								12%	3 w
Radvany P, et al.[19]	1975	Article	USA	Mongrel dogs	n.a.	17–30 kg	n.a.	10%	20 min
Madias JE, et al.(a)[20]	1974	Article	USA	Mongrel dogs	n.a.	23.8 ± 1.1 kg	n.a.	12%	15 min
Madias JE, et al.(b)[20]								8%	15 min
Madias JE, et al.(c)[20]								6%	15 min
Schroll M, et al.(a)[21]	1971	Article	USA	Mongrel dogs	n.a.	8–24 kg	n.a.	12%	10 min
Schroll M, et al.(b)[21]								8%	8 min
Yoshikawa H, et al.(a)[22]	1973	Article	USA	Mongrel dogs	n.a.	n.a.	n.a.	5%	3 min
Yoshikawa H, et al.(b)[22]								5%	6 min
Yoshikawa H, et al.(c)[22]								5%	9 min
Yoshikawa H, et al.(d)[22]								5%	12 min

Table 2. Quality Assessment for Included Studies. +, low risk; -, high risk; ?, unclear

Bias	Study	Nakada Y, et al. (2017)	Hrdlicka J, et al. (2016)	Radvany P, et al. (1975)	Madias JE, et al. (1974)	Schroll M, et al. (1971)	Yoshikawa H, et al. (1973)
Selection bias	Sequence generation	-	+	-	-	-	-
	Baseline characteristics	+	+	+	+	+	+
	Allocation concealment	?	?	-	-	-	-
Performance bias	Random housing	-	+	-	-	-	-
	Blinding for caregivers and researchers	?	?	-	?	?	-
Detection bias	Random outcome assessment	?	?	?	?	?	?
	Blinding for outcome assessors	?	?	?	?	?	?
Attrition bias	Incomplete outcome data	+	+	-	+	-	+
Reporting bias	Selective outcome reporting	+	-	-	+	+	+
Other	Other sources of bias	+	+	+	+	+	+

Improvement in cardiac hemodynamics under acute hypoxia

Reports of canine studies provided data regarding changes in cardiac hemodynamics under acute hypoxia from 10 experiments. A pooled analysis revealed that hypoxia greatly improved various parameters related to cardiac hemodynamics, including the maximal rate of increase in left ventricular pressure (LV dp/dt) (SMD = 1.27; 95% CI, 0.27 to 2.28; P = 0.013), left ventricular end-diastolic pressure (SMD = 1.26; 95% CI, 0.05 to 2.47; P = 0.041), left atrial pressure (LAP) (SMD = 1.20; 95% CI, 0.57 to 1.82; P < 0.001), cardiac output (CO) (SMD = 1.26; 95% CI, 0.34 to 2.18; P = 0.007), total pulmonary resistance (TPR) (SMD = 0.76; 95% CI, 0.20 to 1.33; P = 0.008) and pulmonary arterial mean pressure (PAMP) (SMD = 2.02; 95% CI, 0.23 to 3.81; P = 0.027), while reducing the total systematic vascular resistance (SMD = −0.89; 95% CI, −1.24 to −0.53; P < 0.001). Although the overall analysis also indicated that acute hypoxia increased the arterial pressure (SMD = 0.56; 95% CI, 0.07 to 1.05; P = 0.027), the data lacked robustness further research is needed to confirm this association (Table 3). Comparisons of other hemodynamic outcomes are shown in Table 3. A subgroup analysis stratified by oxygen concentration revealed that a lower oxygen concentration in air induced a higher stroke volume (SV) (P = 0.010, Fig. 3).

Changes in arterial blood gases and infarcted area

Arterial blood gases were measured in three dog studies. Our analyses revealed that acute hypoxia increased the blood pH value (WMD = 0.05; 95% CI, 0.03 to 0.08; P < 0.001) and reduced the arterial partial pressures of carbon dioxide ($PaCO_2$) (WMD = −3.90; 95% CI, −6.06 to −1.74; P < 0.001) and oxygen (PaO_2) (WMD = −41.36; 95% CI, −49.97 to −32.75; P < 0.001). Furthermore, oxygen saturation (SaO_2) was significantly reduced during the early stages of hypoxia (WMD = −16.20; 95% CI, −28.83 to −3.56; P = 0.012; Fig. 5). No significant effect of hypoxia on the area of fibrosis was observed (SMD = −2.53; 95% CI, −6.17 to 1.12; P = 0.175). However, the sensitivity analysis revealed a lack of robustness in this area, indicating the need for additional study. Other outcomes such as body weight are presented in Table 3.

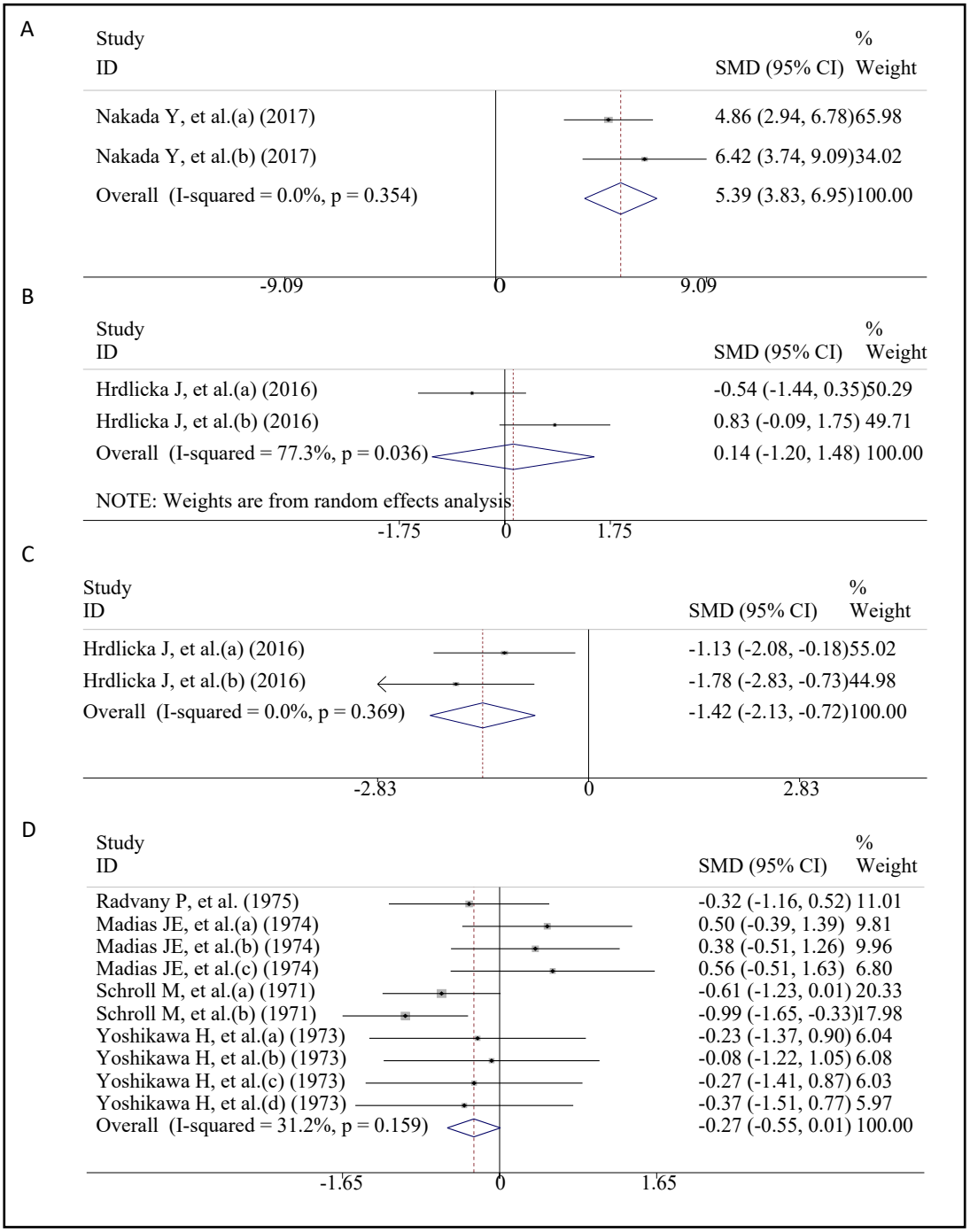

Fig. 2. Effects of hypoxia on cardiac function. The effects of chronic hypoxia on ejection fraction (A) (experiment vs. control, 18 vs. 15), fractional shortening (B) (20 vs. 20) and heart rate (C) (20 vs. 20) and the effect of acute hypoxia on heart rate (D) (103 vs. 103) were determined using data from two, two, two, and 10 experiments, respectively.

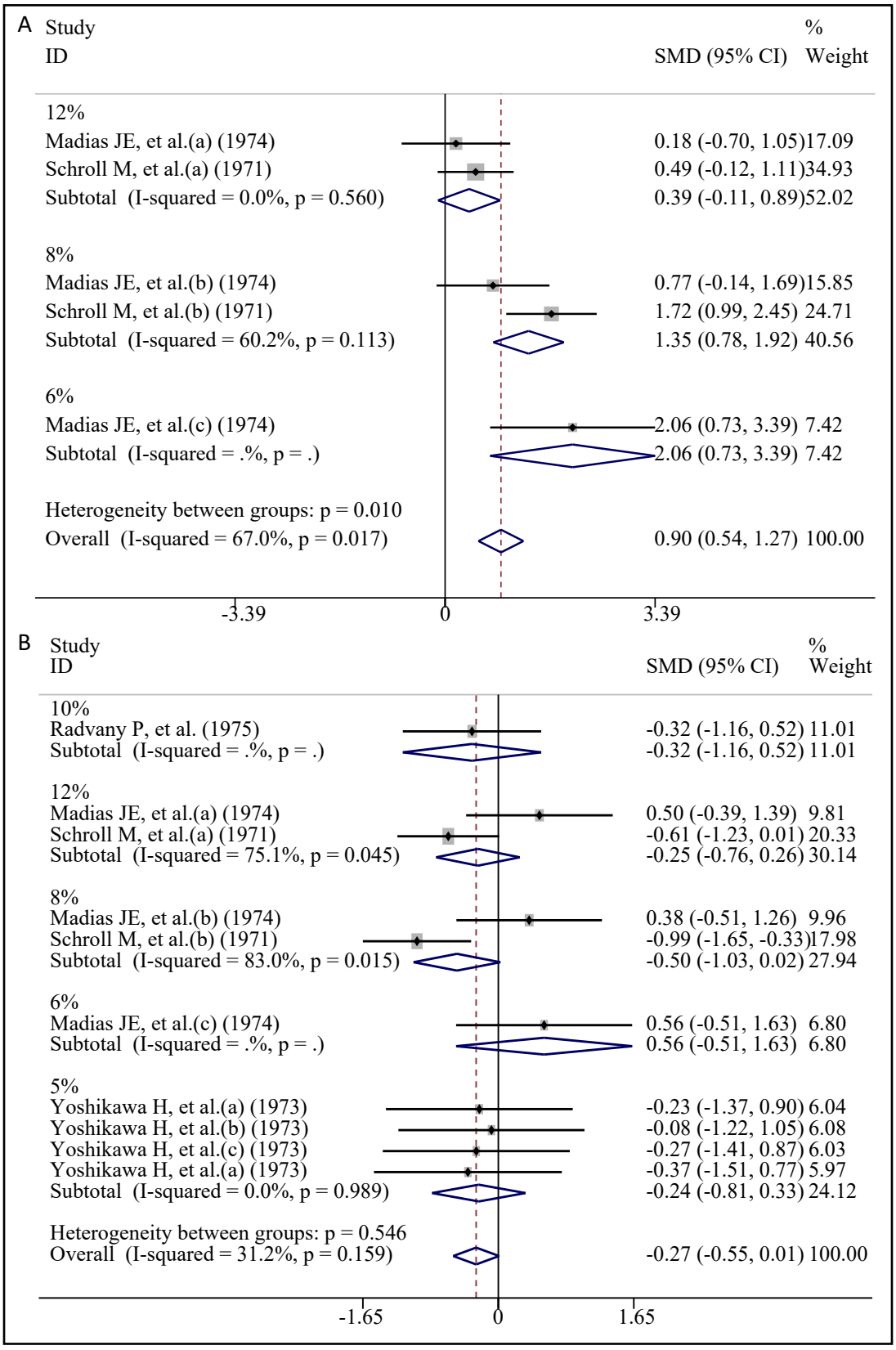

Fig. 3. Subgroup analysis of the effects of hypoxia on (A) stroke volume and (B) heart rate, stratified by oxygen concentration.

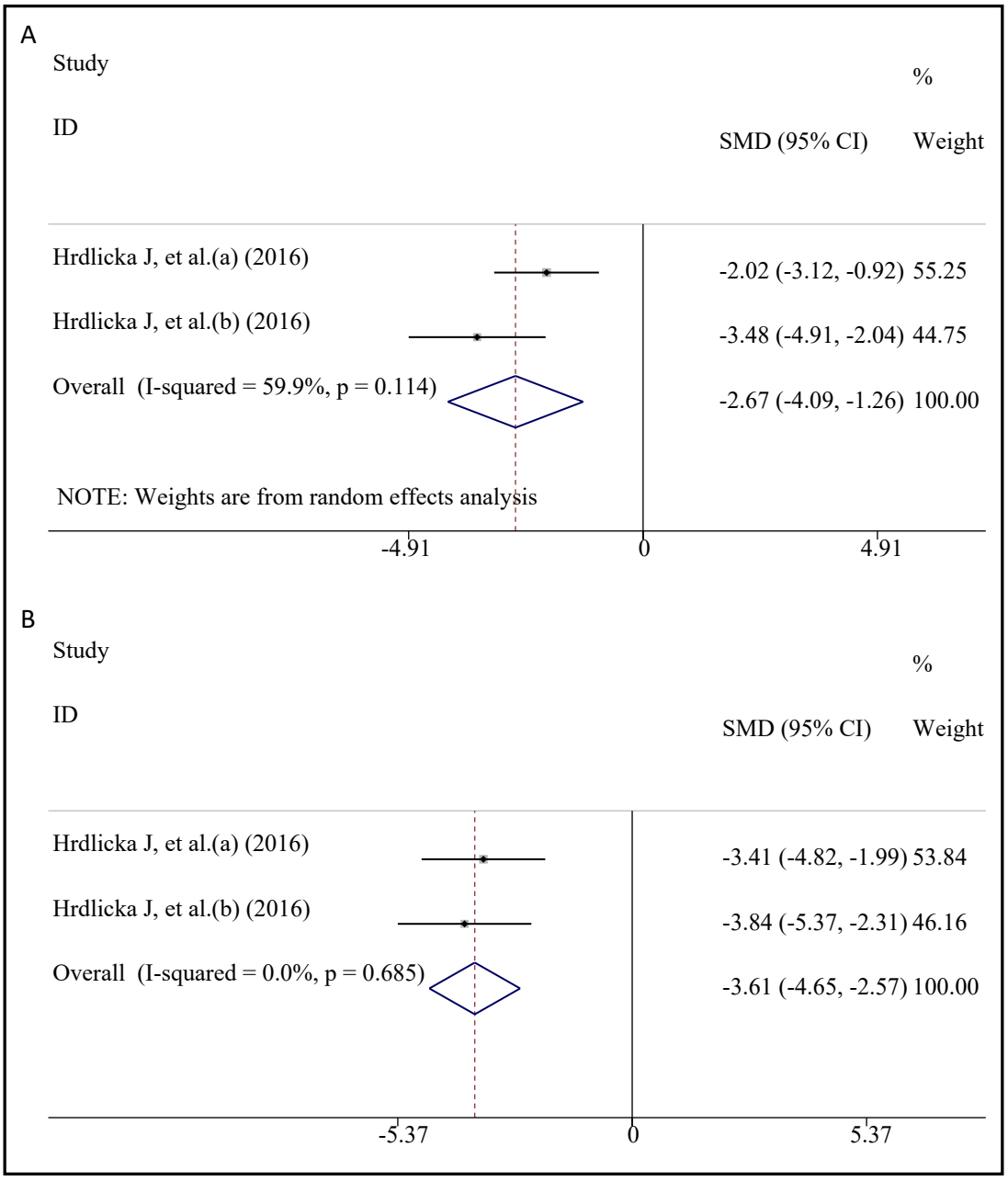

Fig. 4. Effects of hypoxia on arterial blood gases. The effects of acute hypoxia on end-systolic left ventricular diameter (A) (experiment vs. control, 10 vs. 10) and end-diastolic left ventricular diameter (B) were determined using data from two and two experiments, respectively.

Table 3. Meta-analysis of cardiac geometry, hemodynamic and others. PWTs, end-systolic posterior wall thickness; PWTd, end-diastolic posterior wall thickness; AWTs, end-systolic anterior wall thickness; AWTd, end-diastolic anterior wall thickness; LVDs, end-systolic left ventricular diameter; LVDd, end-diastolic left ventricular diameter; MLAP, mean left atrial pressure; LAP, left atrial pressure; LV dp/dt, the maximal rate of rise of left ventricular pressure; LVEDP, left ventricular end-diastolic pressure; LVSP, left ventricular systolic pressure; MAoF, mean aorta flow; ASP, aortic systolic pressure; AMP, aortic mean pressure; AP, arterial pressure; SV, stroke volume; CO, cardiac output; TSVR, total systemic vascular resistance; TPR, total pulmonary resistance; PAMP, pulmonary arterial mean pressure. a Sensitive analyse was done by using the random-effect and fixed-effect model

Outcomes		animal	Included experiment NO.	I^2	Effect size (95%CI)	P value	Sensitive analyse [a]	
							Fixed	Random
Cardiac geometry under chronic hypoxia	PWTs	rat	2	1.4	SMD = 0.59 (-0.05, 1.23)	0.071	0.59 (-0.05, 1.23)	0.59 (-0.05, 1.23)
	PWTd	rat	2	35.8	SMD = 0.00 (-0.63, 0.63)	1.000	0.00 (-0.63, 0.63)	0.00 (-0.78, 0.78)
	AWTs	rat	2	0.0	SMD = 0.06 (-0.56, 0.68)	0.852	0.06 (-0.56, 0.68)	0.06 (-0.56, 0.68)
	AWTd	rat	2	0.0	SMD = -0.24 (-0.86, 0.39)	0.455	-0.24 (-0.86, 0.39)	-0.24 (-0.86, 0.39)
	LVDs	rat	2	59.9	SMD = -2.67 (-4.09, -	0.000	-2.56 (-3.43, -	-2.67 (-4.09, -
	LVDd	rat	2	0.0	SMD = -3.61 (-4.65, -	0.000	-3.61 (-4.65, -	-3.61 (-4.65, -
Cardiac hemodynamics under acute hypoxia	MLAP	dog	2	94.8	SMD = 0.88 (-1.26, 3.03)	0.421	0.65 (0.17, 1.12)	0.88 (-1.26, 3.03)
	LAP	dog	4	0.0	SMD = 1.20 (0.57, 1.82)	0.000	1.20 (0.57, 1.82)	1.20 (0.57, 1.82)
	LV dp/dt	dog	5	84.5	SMD = 1.27 (0.27, 2.28)	0.013	1.11 (0.72, 1.49)	1.27 (0.27, 2.28)
	LVEDP	dog	5	88.8	SMD = 1.26 (0.05, 2.47)	0.041	1.28 (0.88, 1.68)	1.26 (0.05, 2.47)
	LVSP	dog	2	91.8	SMD = 0.45 (-1.15, 2.05)	0.580	0.37 (-0.09, 0.82)	0.45 (-1.15, 2.05)
	MAoF	dog	2	81.0	SMD = 0.89 (-0.18, 1.95)	0.103	0.83 (0.37, 1.29)	0.89 (-0.18, 1.95)
	ASP	dog	2	90.9	SMD = 0.36 (-1.35, 2.07)	0.681	0.13 (-0.36, 0.62)	0.36 (-1.35, 2.07)
	AMP	dog	5	79.1	SMD = 0.65 (-0.18, 1.47)	0.123	0.35 (-0.00, 0.70)	0.65 (-0.18, 1.47)
	AP	dog	5	49.8	SMD = 0.56 (0.07, 1.05)	0.027	0.56 (0.07, 1.05)	0.52 (-0.18, 1.22)
	SV	dog	5	67.0	SMD = 0.97 (0.31, 1.64)	0.004	0.90 (0.54, 1.27)	0.97 (0.31, 1.64)
	CO	dog	3	55.3	SMD = 1.26 (0.34, 2.18)	0.007	1.14 (0.54, 1.73)	1.26 (0.34, 2.18)
	TSVR	dog	5	10.9	SMD = -0.89 (-1.24, -	0.000	-0.89 (-1.24, -	-0.89 (-1.27, -
	TPR	dog	3	32.7	SMD = 0.76 (0.20, 1.33)	0.008	0.76 (0.20, 1.33)	0.78 (0.09, 1.48)
	PAMP	dog	3	84.1	SMD = 2.02 (0.23, 3.81)	0.027	1.39 (0.75, 2.04)	2.02 (0.23, 3.81)
Others	Fibrosis	mice,	2	90.7	SMD = -2.53 (-6.17, 1.12)	0.175	-1.47 (-2.35, -	-2.53 (-6.17, 1.12)
	Body weight	rat	2	0.0	SMD = -1.29 (-1.98, -	0.000	-1.29 (-1.98, -	-1.29 (-1.98, -

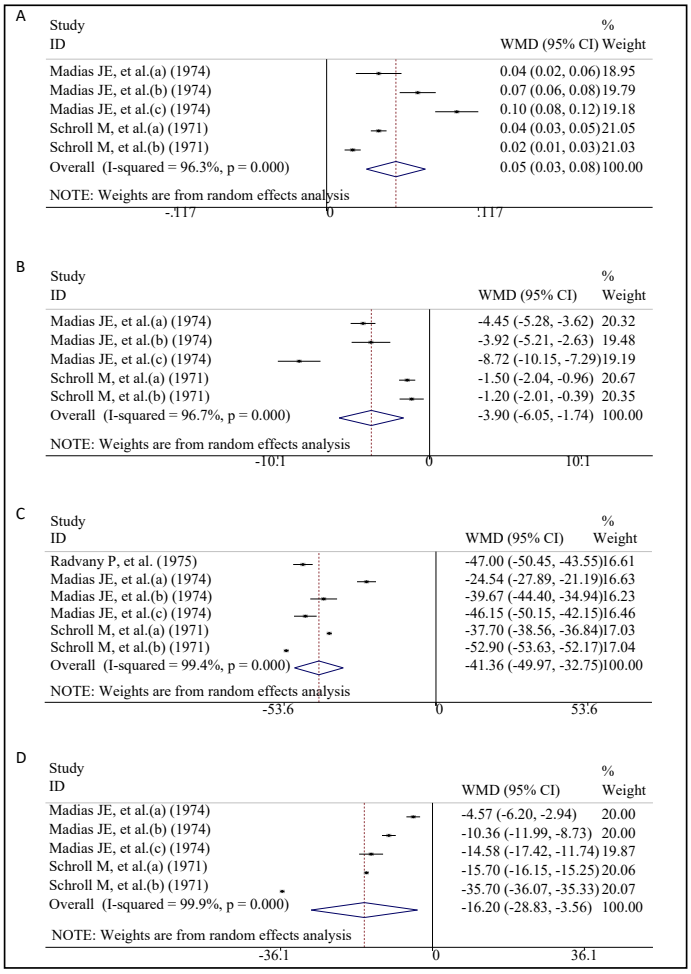

Fig. 5. Effects of hypoxia on cardiac function. The effects of acute hypoxia on pH (A) (experiment vs. control, 68 vs. 68), arterial partial pressure of carbon dioxide (B) ($PaCO_2$, 68 vs. 68), arterial partial pressure of oxygen (C) (PaO_2, 79 vs. 79) and oxygen saturation (D) (SaO_2, 68 vs. 68) were based on data from five, five, six, and five experiments, respectively. The weighted mean difference and corresponding 95% confidence interval (CI) were applied to each variable.

Discussion

Our meta-analysis suggests that chronic hypoxia has beneficial effects on infarcted heart function, such as EF enhancement, whereas acute hypoxia significantly improves hemodynamics as indicated by the increases in LV dp/dt and CO and the decrease in total systematic vascular resistance. In addition, a lower oxygen content can significantly increase SV during the early stages of environmental hypoxia. However, hypoxia also reduces the LVDs and LVDd and increases TPR, PAMP, and LAP, which can aggravate pulmonary edema. Despite these drawbacks, the ability of systematic hypoxia to enhance overall cardiac function suggests that its benefits exceed its disadvantages.

Hypoxic pulmonary vasoconstriction, an adaptation of hypoxia, augments the TPR and consequently increases the PAMP and LAP, which has a detrimental effect on pulmonary circulation, leading to pulmonary edema. The lower body weight in the hypoxia group (Table 3) may lead to the attenuation of LV dilatation [23], which in turn reduces the demand for energy in the LV. However, similar studies in an model of MI exposed to chronic intermittent hypobaric hypoxia did not indicate a reduction in body weight [24], suggesting that a lower body weight is not the primary reason for the attenuation of LV dilatation.

The positive effect of hypoxia on cardiac repair is counterintuitive, given the frequent administration of supplemental oxygen to patients with MI with hypoxemia to correct the latter condition and recover cardiac function. In addition, the specific mechanism underlying protective hypoxia remains unclear. In this analysis, the pooled outcomes of PaO_2 and SaO_2 indicated only mild hypoxemia in animal models of MI, consistent with previous animal studies of chronic continuous hypoxia [7, 19]. Several studies have reported that hypoxia-mediated reactive oxygen species (ROS) can contribute to tissue adaptation and repair [7, 25], thus suggesting that moderate hypoxemia can sustain the moderate level of ROS needed to enhance the injury-repair response. Consistent with this speculation, previous studies determined that ROS have both beneficial and detrimental effects that depend largely on the level, source, and compartmentalization [26, 27].

Similar to ROS, moderate hypoxia was found to confer many benefits, including the promotion of angiogenesis [28], regeneration of tissue [7], and increased in anaerobic metabolism [29]. Hypoxia-induced angiogenesis can increase the delivery of oxygen to infarcted cardiomyocytes, whereas increased anaerobic metabolism produces more energy to support cardiac repair. Initially, environmental hypoxia appears to improve cardiac hemodynamics via these mechanisms, whereas continuous chronic hypoxia accumulates these benefits, resulting in significant cardiac function recovery. Therefore, the advantages of mild hypoxemia should be considered when administering supplemental oxygen to patients with MI.

Limitations

This review had some limitations of note. First, the inclusion of only six studies limited the experimental data available for the subgroup analyses. However, the relevant references from the included studies had been scrutinized in an attempt to obtain additional evidence for the effects of hypoxia in MI models. Second, the studies varied with respect to measurement methods and units, which contributed to the high level of heterogeneity in the partial outcomes. Third, the pooled results included data of several species. To eliminate species-related effects, we standardized each outcome by applying the SMD. Meanwhile, the low level of heterogeneity in the primary outcomes, except the heart rate under chronic hypoxia, demonstrated that the pooled results were species-independent. Therefore, we performed subgroup analyses despite the limited number of included experiments. Finally, the durations of hypoxia ranged from 3 minutes to 3 weeks, and the studies were therefore classifiable into acute and chronic hypoxia groups. Despite this, we observed the effects of various durations of hypoxia according to the heterogeneity of the results (Fig. 3, 5). Accordingly, a sensitivity analysis was applied to test the robustness of the outcomes. All outcomes with high heterogeneity were determined to be robust, implying that the duration

of hypoxia did not influence the final conclusions. Finally, the effects of covariates relevant to the results may have been confounded by the effects of other covariates not included in this analysis.

Implications for clinical practice

Our study suggests that a reduction in environmental oxygen can greatly improve various parameters of heart function after MI, including hemodynamics during early-stage hypoxia and systolic function during chronic hypoxia. These findings from animal studies lead us to recommend the performance of large-scale, multicenter randomized controlled trials to determine the effects of a mildly hypoxic environment on MI patients with mild or no hypoxemia. In addition, updates to clinical practice guidelines might consider the evidence presented herein.

Implications for basic research

Further research is needed to determine the long-term effects of hypoxia on cardiac hemodynamics and the optimal inspired oxygen concentration. Larger, more rigorous studies of hypoxia would be expected to provide more powerful information about cardiac fibrosis and structural changes. The specific mechanisms that underlie the protective effects of acute and chronic hypoxia should also be clarified to yield a better understanding of the indications and considerations of hypoxia.

Conclusion

According to the current evidence, hypoxia plays a largely beneficial role in heart function recovery after myocardial infarction, with effects such as enhanced EF under chronic hypoxia and improved hemodynamics under acute hypoxia. However, it has slightly detrimental effects on pulmonary circulation and left ventricular geometry. In addition, the finding that a lower inspired oxygen concentration can significantly augment SV suggests the need for further research to determine the optimal level of hypoxia.

Disclosure Statement

The authors declare no conflicts of interest.

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