

Dose-dependent scavenging activity of the ultra-short-acting β 1-blocker landiolol against specific free radicals

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Landiolol, a highly cardioselective ultra-short-acting β 1-blocker, prevents perioperative atrial fibrillation associated with systemic inflammation and oxidative stress. We evaluated the direct scavenging activity of landiolol against multiple free radical species. Nine free radical species (hydroxyl, superoxide anion, ascorbyl, *tert*-butyl peroxy, *tert*-butoxy, singlet oxygen, 2,2-diphenyl-1-picrylhydrazyl, nitric oxide, and tyrosyl radicals) were directly quantified using an X-band ESR spectrometer with the spin-trapping method. IC_{50} and reaction rate constants were estimated from the dose-response curve for each free radical. Landiolol scavenged six of the free radical species examined: hydroxyl radical ($IC_{50} = 0.76$ mM, $k_{landiolol} = 1.4 \times 10^{10} M^{-1} s^{-1}$, $p < 0.001$), superoxide anion (58 mM, $2.1 M^{-1} s^{-1}$, $p = 0.044$), *tert*-butoxy radical (4.3 mM, $k_{landiolol}/k_{CYPMPO} = 0.77$, $p < 0.001$), ascorbyl free radical (0.31 mM, $p < 0.001$), singlet oxygen (0.69 mM, $k_{landiolol}/k_{4-OH TEMP} = 2.9$, $p < 0.001$), and nitric oxide (15 mM, $1.7 \times 10 M^{-1} s^{-1}$, $p < 0.001$). This study is the first to report that landiolol dose-dependently scavenges multiple free radical species with different reaction rate constants. These results indicate the potential clinical application of landiolol as an antioxidative and anti-inflammatory agent in addition to its present clinical use as an anti-arrhythmic agent.

Key Words: landiolol, free radical species, antioxidative, anti-inflammatory, anti-arrhythmic

Perioperative atrial fibrillation (POAF) is associated with an increased long-term risk of ischemic stroke.⁽¹⁾ Its prevention is of clinical importance in anesthesia management. The pathophysiology of POAF is associated with systemic inflammation,⁽²⁾ ischemia,⁽³⁾ and oxidative stress.⁽⁴⁻⁶⁾

Landiolol (ONO-1101, ONOACT[®]; C₂₅H₃₉N₃O₈·HCl, MW 546.05, CAS 133242-30-5; Fig. 1) is a highly cardioselective ultra-short-acting β 1-blocker. It has been clinically used to control rapid heart rate in patients with atrial fibrillation and atrial flutter in the perioperative period⁽⁷⁾ and with recurrent hemodynamically unstable ventricular tachycardia.⁽⁸⁾ Intraoperative and perioperative administration of low-dose landiolol has a preventive effect on the appearance of atrial fibrillation after coronary artery bypass graft (CABG) surgery,⁽⁹⁾ esophagectomy for cancer,⁽¹⁰⁾ and pulmonary resection for lung cancer.⁽¹¹⁾

Landiolol prevents not only POAF but also inflammation.⁽¹²⁻¹⁵⁾ In one report, landiolol successfully managed tachycardiac atrial fibrillation in a septic patient.⁽¹²⁾ In addition, landiolol ameliorates lipopolysaccharide-induced systemic inflammation.⁽¹⁶⁾

Although some studies have reported the antioxidative activity of landiolol,⁽¹⁷⁾ the detailed mechanisms are not fully understood. To the best of our knowledge, there are no data available

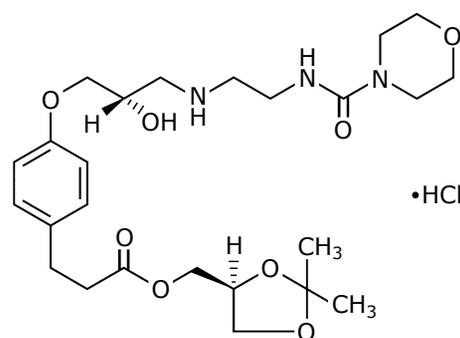


Fig. 1. Chemical structures of landiolol (ONO-1101, MW 546.05, CAS 133242-30-5).

concerning its direct scavenging activity against specific free radicals. Thus, this study aimed to illustrate the dose-response relationships of the direct scavenging activity of landiolol against multiple free radical species generated *in vitro*.

Materials and Methods

Materials. ONO-1101, an active ingredient of landiolol, was obtained from Ono Pharmaceutical Co. Ltd (Osaka, Japan). *tert*-Butyl hydroperoxide and 2,2-diphenyl-1-picrylhydrazyl (DPPH) were purchased from Sigma-Aldrich (St. Louis, MO). 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO), *N*-methyl-3-(1-methyl-2-hydroxy-2-nitrosohydrazino)-1-propanamine (NOC7), and 2-(4-carboxyphenyl)-4,4,5,5-tetramethylimidazolin-1-oxyl 3-oxide (carboxy-PTIO) were purchased from Dojindo (Kumamoto, Japan). 2-[5,5-Dimethyl-2-oxo-2 λ 5-(1,3,2) dioxaphosphan-2-yl]-2-methyl-3,4-dihydro-2*H*-pyrrole 1-oxide (CYPMPO) was purchased from Mikuni Pharmaceutical Industrial (Osaka, Japan). Sodium ascorbate, dimethyl sulfoxide, and hydrogen peroxide were purchased from Wako Pure Chemical Industries (Osaka, Japan). 2,2'-Azobis (2-amidinopropane) dihydrochloride (AAPH), Acid Red 94, and 4-hydroxy-2,2,6,6-tetramethylpiperidine (4-OH TEMP) were purchased from Tokyo Chemical Industry (Tokyo, Japan). The other reagents used were of the highest commercially available quality.

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Electron spin resonance spectrometry. Electron spin resonance (ESR) spectrometry was conducted as previously described.^(18–20) Free radicals were quantified using an X-band ESR spectrometer (JES-RE1X; JEOL, Tokyo, Japan) with the operation software WIN-RAD ver. 1.20b (Radical Research Inc., Tokyo, Japan). The ultraviolet (UV)/visible (VIS) light source was a 200-W medium-pressure mercury/xenon arc (UVF-203S; San-Ei Electric, Osaka, Japan) with either a UV-transmitting-VIS-absorbing or a VIS-transmitting-UV-absorbing filter, where UV or VIS light was guided through a quartz light guide into the ESR sample cavity. Free radicals were produced in disposable ESR flat cells (Radical Research). The typical instrument settings were as follows: room temperature (23°C); frequency 9.45 GHz with 100-kHz modulation; modulation width, 0.1 mT; time constant, 0.1 s; center field, 335.8 mT; sweep width, 7.5 mT; sweep time, 1 min. The microwave power was set such that the ESR signals were not saturated (4 mW).

Table 1 lists the production and trapping methods for the nine free radicals examined. Briefly, hydroxyl radicals were produced using a Fenton-type reaction and trapped with CYPMPO.⁽²¹⁾ Superoxide anions were generated by UV irradiation of a concentrated hydrogen peroxide aqueous solution and trapped with CYPMPO.⁽²¹⁾ An alkyl peroxy radical, *tert*-butyl peroxy, was produced by UV irradiation of *tert*-butyl hydroperoxide and trapped with CYPMPO.⁽²¹⁾ The *tert*-butoxyl radical was generated by UV irradiation of 1 mM AAPH and trapped with CYPMPO.⁽²¹⁾ Ascorbyl free radicals were produced from sodium ascorbate by adding 99% dimethyl sulfoxide.⁽²²⁾ Singlet oxygen was generated by VIS light irradiation of Acid Red 94 with its quencher 4-OH TEMP, forming the 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPOL).⁽²¹⁾ DPPH was directly observed using ESR. The nitric oxide radical was produced from NOC7 reacted with carboxy-PTIO, generating carboxy-PTI, which was measured 60 min after mixing.⁽²¹⁾ The tyrosyl radical was generated from hemoglobin by adding hydrogen peroxide and trapped with DMPO.⁽²³⁾

The third and fourth ESR signals of manganese (II) oxide (MnO) were used as external references for the ascorbyl free radical, DPPH, nitric oxide, and the tyrosyl radical, and the second and fifth for CYPMPO-spin adducts. The intensity of the free radical signal was quantified as the ratio of the signal intensity to that of MnO, and then standardized relative to the control ESR signal with no landiolol added.

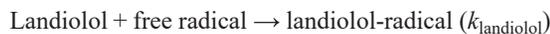
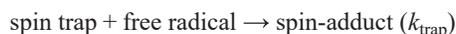
Calculation of 50% inhibitory concentration. Dose-response curves were nonparametrically calculated by fitting data to a sigmoid curve:⁽²⁴⁾

$$y = \frac{1}{1 + \left(\frac{x}{a}\right)^b}$$

where *a* gives the estimation of 50% inhibitory concentration (IC₅₀), *x* is the final concentration of landiolol [M], and *y* is the

observed free radical activity relative to the control.

Estimation of reaction rate constants. According to a kinetic competition model, the following competitive reactions occur in the reaction mixture:⁽²⁵⁾



where *k*_{trap} and *k*_{landiolol} are the second-order rate constants. The reaction rate constant *k*_{landiolol} is expressed as follows:

$$k_{\text{landiolol}} = \frac{[\text{spin trap}]}{\text{IC}_{50}} k_{\text{trap}}$$

*k*_{trap} values used were as follows: *k*_{CYPMPO} for hydroxyl radical $4.2 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$,⁽²⁶⁾ *k*_{CYPMPO} for superoxide anion $48 \text{ M}^{-1} \text{ s}^{-1}$,⁽²⁶⁾ and *k*_{carboxy-PTIO} for nitric oxide $1.01 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$.^(27,28) Because *k*_{CYPMPO} for *tert*-butyl hydroperoxide and the *tert*-butoxyl radical have not been reported, *k*_{landiolol} for those free radicals were presented as relative values to *k*_{CYPMPO}.

TBARS assay. Peroxidation of rat brain homogenate was assessed using a thiobarbituric acid (TBA) reactive substance (TBARS) assay.⁽²⁹⁾ Brain tissue was employed because it is rich in lipids. The reaction mixture contained 0.3 ml homogenate in 30 volumes Tris-HCl buffer (20 mM, pH 7.4) and 0.1 ml of saline or landiolol dissolved in saline. Peroxidation was initiated by (1) the hydroxyl radical by adding 0.1 ml of FeCl₃ (100 mM), or (2) carbon-centered radicals by adding 0.1 ml of FeCl₃ (100 mM) plus 0.05 ml of 1 mM ascorbate. After incubation for 20 min at 37°C, the final product of lipid peroxidation (malondialdehyde, MDA) was reacted with TBA in boiled water for 15 min, and the adduct was quantified at 535 nm (Thermo Scientific™ Multiskan GO microplate spectrophotometer; Thermo Fisher Scientific, Vantaa, Finland).

Statistical analysis. Statistical tests were performed by the statistical software R ver. 3.6.3 (<https://www.R-project.org/>). Values are presented as mean ± 95% confidence interval. The significance level was set at *p* < 0.05.

Results

The ESR spectra of the spin adducts for each radical examined are shown in Fig. 2. Each spectrum was assigned to the corresponding free radical by the hyperfine splitting constants (Table 2).

Hydroxyl radical. Landiolol scavenged hydroxyl radicals in a dose-dependent manner (Fig. 2A). The IC₅₀ was $0.76 \pm 0.07 \text{ mM}$ (*p* < 0.001). Since the reaction rate constant of CYPMPO (*k*_{G-CYPMPO}) for the hydroxyl radical is already known, *k*_{landiolol} was estimated to be $1.4 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ (*k*_{landiolol}/*k*_{CYPMPO} = 3.3).

Superoxide anion. Landiolol directly scavenged superoxide anions in a dose-dependent manner (Fig. 2B, IC₅₀ = $58 \pm 24 \text{ mM}$, *p* = 0.044). *k*_{landiolol} was estimated to be $2.1 \text{ M}^{-1} \text{ s}^{-1}$ (*k*_{landiolol}/*k*_{CYPMPO} = 0.04).

Table 1. Generation of free radicals

Free radical species	Precursor/sensitizer	Spin trap/quencher
Hydroxyl radical	0.2 mM Fe ²⁺ + 0.15% (44 mM) hydrogen peroxide (Fenton-type reaction)	2.5 mM CYPMPO
Superoxide anion	24% (7 M) hydrogen peroxide + UV 1 s	2.5 mM CYPMPO
<i>tert</i> -Butyl peroxy radical	180 mM <i>tert</i> -butyl hydroperoxide + UV 10 s	0.8 mM CYPMPO
<i>tert</i> -Butoxyl radical	1 mM AAPH + UV 1 s	3.3 mM CYPMPO
Ascorbyl free radical	0.01 mg/ml (50 μM) sodium ascorbate + 99% DMSO	—
Singlet oxygen	Acid red (200 μM) + 500–600 nm light 60 s	2 mM 4-OH TEMP
Nitric oxide	250 μM NOC7	25 μM carboxy-PTIO
DPPH	15 μM DPPH	—
Tyrosyl radical	0.16 mM myoglobin + 0.003% (0.9 mM) hydrogen peroxide	0.9 M DMPO

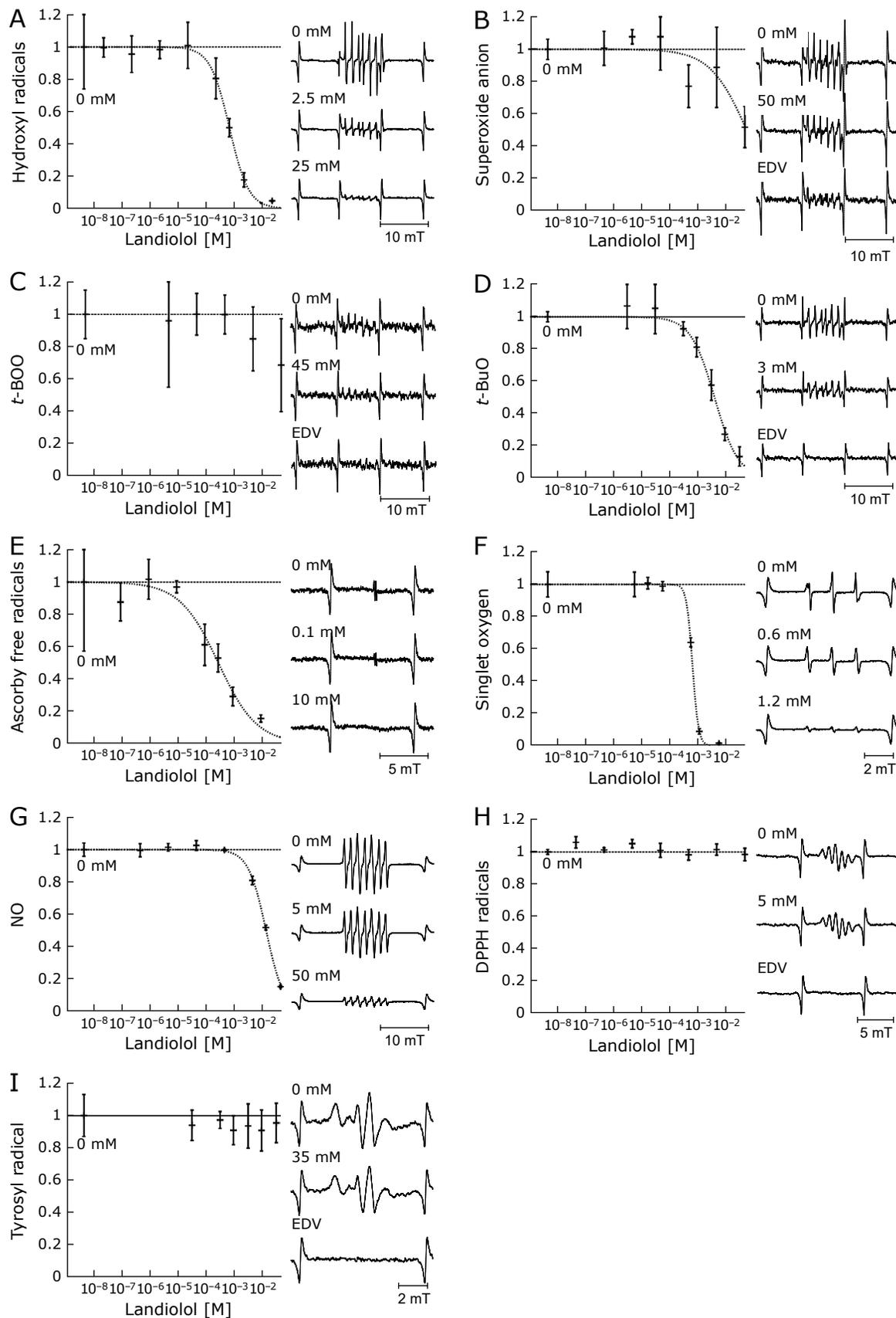


Fig. 2. Electron spin resonance (ESR) spectra of free radicals and dose-response curves of direct scavenging activity of landiolol against multiple free radicals. Landiolol dose-dependently scavenged hydroxyl radical (A), superoxide anion (B), *tert*-butoxyl radical (D), ascorbyl free radical (E), singlet oxygen (F), and nitric oxide (G). Landiolol scavenged *tert*-butyl peroxy radical at 45 mM ($p = 0.03$, C). However, it did not show radical-scavenging activity against DPPH (H) and tyrosyl radical (I). Signals on both ends of each spectrum are those of the external standard of Mn^{2+} . Error bars indicate 95% confidence intervals.

Table 2. Half-maximal inhibitory concentrations (IC_{50}) and relative reaction rate constants of landiolol against multiple free radicals

Free radical species	hfsc [mT]	IC_{50} [M]	Relative reaction rate constants	p value
	$a_{H\cdot}$, $a_{N\cdot}$, a_P			
Hydroxyl radical	1.37, 1.37, 4.88 1.23, 1.35, 4.70	7.6×10^{-4}	$3.3 \times k_{CYPMPO}$	<0.001
Superoxide anion	1.11, 1.26, 5.25 1.04, 1.27, 5.10	5.8×10^{-2}	$0.040 \times k_{CYPMPO}$	0.044
<i>tert</i> -Butyl peroxy radical	1.35, 1.45, 5.05	1.9×10^{-1}	$0.0040 \times k_{CYPMPO}$	0.281
<i>tert</i> -Butoxy radical	1.24, 1.36, 4.80	4.3×10^{-3}	$0.77 \times k_{CYPMPO}$	<0.001
Ascorbyl free radical	0.186, –, –	3.1×10^{-4}	—	<0.001
Singlet oxygen	–, 1.50, –	6.9×10^{-4}	$2.9 \times k_{4-OHTEMP}$	<0.001
Nitric oxide	a_{N1} 0.981, a_{N2} 0.445	1.5×10^{-2}	$0.0016 \times k_{cPTIO}$	<0.001
DPPH	–, 0.903, –	—	—	—
Tyrosyl radical	?	—	—	—

hfsc, hyperfine splitting constants.

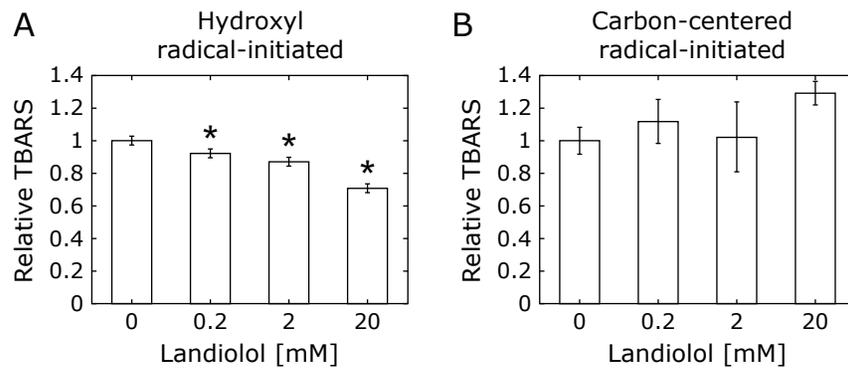


Fig. 3. Antioxidative activity of landiolol by the thiobarbituric acid reactive substance (TBARS) assay initiated by hydroxyl radical (A) and carbon-centered radical (B). Landiolol dose-dependently inhibited peroxidation initiated by hydroxyl radicals (A; * $p < 0.05$ with Bonferroni's correction), while it had no inhibitory effect on peroxidation initiated by carbon-centered radicals (B). Error bars indicate 95% confidence intervals.

***tert*-Butyl peroxy radical.** Landiolol did not successfully scavenge *tert*-butyl peroxy radicals; the estimated IC_{50} (1.9×10^2 mM) was not statistically significant (Fig. 2C, $p = 0.281$).

***tert*-Butoxy radical.** Landiolol significantly scavenged the *tert*-butoxy radical in a dose-dependent manner (Fig. 2D, $IC_{50} = 4.3 \pm 0.4$ mM, $p < 0.001$). $k_{landiolol}/k_{CYPMPO}$ was estimated to be 0.77.

Ascorbyl free radical. Landiolol directly scavenged ascorbyl free radicals in a dose-dependent manner (Fig. 2E, $IC_{50} = 0.31 \pm 0.06$ mM, $p < 0.001$).

Singlet oxygen. Landiolol dose-dependently scavenged singlet oxygen with an IC_{50} of 0.69 ± 0.01 mM (Fig. 2F, $p < 0.001$). $k_{landiolol}/k_{4-OHTEMP}$ was estimated to be 2.9.

Nitric oxide. Landiolol scavenged nitric oxide in a dose-dependent manner (Fig. 2G, $IC_{50} = 15 \pm 0$ mM, $p < 0.001$). $k_{landiolol}$ was estimated to be $1.7 \times 10 M^{-1} s^{-1}$ ($k_{landiolol}/k_{cPTIO} = 1.6 \times 10^{-3}$).

DPPH. Landiolol did not scavenge the artificial free radical DPPH at all (Fig. 2H).

Tyrosyl radical. Landiolol did not scavenge tyrosyl radicals at all (Fig. 2I).

TBARS. Landiolol inhibited lipid peroxidation initiated by hydroxyl radicals in a dose-dependent manner (Fig. 3A), but did not inhibit peroxidation initiated by carbon-centered radicals (Fig. 3B).

Discussion

Landiolol dose-dependently scavenged six of the nine free radical species examined (Table 2, Fig. 3). In addition, landiolol dose-dependently inhibited lipid peroxidation initiated by hydroxyl radicals, but did not inhibit peroxidation initiated by

carbon-centered radicals (Fig. 3).

The presence of chronic atrial fibrillation confers a three-fold increased risk of stroke;⁽¹⁾ thus, perioperative prevention of POAF is clinically important. The mechanisms underlying POAF include oxidative stress in atrial myocytes.⁽³⁰⁾ Patients with atrial fibrillation after surgery had a significantly increased atrial NADPH oxidase activity compared to patients who remained in sinus rhythm.⁽³¹⁾ Atrial fibrillation increased superoxide anion production in both the left atrium and left atrial appendage. An increase in NAD(P)H oxidase and xanthine oxidase activities contributes to increased superoxide anion production in the atrium.⁽³²⁾ A membrane-bound gp91^{phox}/nox2 containing NAD(P)H oxidase is the main source of superoxide production in human atrial myocytes.⁽³³⁾ It has been indicated that atrial NADPH oxidase activity is independently associated with an increased risk of POAF.

Based on these findings, the effects of antioxidants on POAF have been intensively investigated. For example, supplementation with *n*-3 polyunsaturated fatty acids, vitamin C, and vitamin E has been shown to significantly decrease atrial fibrillation, attenuate biomarkers of inflammation and oxidative stress, and increase the activity of catalase, superoxide dismutase, and glutathione peroxidase in atrial tissue. In addition, POAF significantly increases mRNA expression of NADPH oxidase p47-phox subunit protein in atrial tissue.⁽³⁴⁾ A meta-analysis has demonstrated that patients treated with antioxidants, ascorbate, or *N*-acetylcysteine showed a significant reduction in POAF.⁽³⁵⁾ Perioperative control of the heart rate by β 1-blockers improved the postoperative prognosis. For example, heart rate control with the short-acting β 1-blocker esmolol improved mortality in patients

with septic shock.⁽³⁶⁾ Through its free radical scavenging effect, a nonselective β -blocker, carvedilol, prevented the redox-dependent increase in intracellular Ca^{2+} as an antioxidant in addition to its action as a stabilizer of the ryanodine receptor in heart failure.⁽³⁷⁾

Plasma norepinephrine concentration is positively correlated to the subsequent risk of mortality.⁽³⁸⁾ In an animal experiment, isoproterenol (ISO), a β -adrenergic agonist, increased mitochondrial reactive oxygen species (ROS) production in cardiomyocytes.⁽³⁹⁾ Thus, it is speculated that β -blockers could inhibit oxidative stress indirectly. We acquired unpublished data on the dose-dependent scavenging activity of the selective β 1-blocker esmolol and non-selective β -blockers (propranolol, alprenolol) against hydroxyl radicals, whose IC_{50} was in a similar order as that of landiolol (0.91 mM, 0.29 mM, 0.38 mM and 0.76 mM for esmolol, propranolol, alprenolol and landiolol, respectively using the same experimental protocol). This may indicate that the radical scavenging activity is independent of the selectivity of β -blockers. Given the radical scavenging activities are similar, selective β 1-blockers could be better applied clinically. Particularly, landiolol should be efficient with its more potent negative chronotropic effect and its lower influence on the blood pressure as compared to esmolol.^(40,41)

In patients with septic shock, esmolol was shown to significantly reduce heart rates without increased adverse events, leading to an improved prognosis.⁽³⁶⁾ Esmolol infusion reduced inflammatory cytokine tumor necrosis factor- α concentrations and improved mortality, cardiac output, and cardiac efficiency.⁽⁴²⁾ In addition to hemodynamic optimization, anti-inflammatory and antioxidative effects should be considered as possible pathophysiological mechanisms of esmolol.

In a rat model of endotoxin-induced sepsis, landiolol has been found to be protective against acute lung injury and cardiac dysfunction associated with its anti-inflammatory activity, including a significant reduction in serum levels of the inflammation mediator HMGB-1 and histological lung damage.⁽¹⁸⁾ Landiolol rapidly attenuates the heart rate without lowering the blood pressure; therefore, landiolol can be used safely without hemodynamic complications.⁽⁴³⁾ Recently, the efficacy and safety of landiolol for treatment of sepsis-related tachyarrhythmias under an appropriate monitoring of the blood pressure and heart rate was confirmed in a randomized controlled trial.⁽⁴⁴⁾ In addition to its safety and effectiveness, the prevention of POAF with landiolol is highly cost-effective.⁽⁴⁵⁾ The present study is the first to demonstrate that landiolol directly scavenges multiple free radicals. Thus, in addition to negative chronotropic action and an anti-inflammatory effect, it is speculated that the multiple free radical scavenging activity of landiolol significantly contributes to the inhibition of POAF.

The present study has some limitations. First, we must elucidate the equilibrium of landiolol in the body. After intravenous administration, landiolol acts as a cardioselective β -blocker in the extracellular fluid. However, in ischemia/reperfusion injury, free radicals are generated in the intracellular fluid or in the matrix of mitochondria *in vivo*. Intracellular pharmacodynamics should be more detailed. Second, the present study evaluated the free radical scavenging activity of landiolol in solutions with only a few varieties of solute species. The possible influence of intracellular and intramitochondrial electrolytes, proteins, and other

metabolites on scavenging activity were not considered in the present study. Third, landiolol is rapidly hydrolyzed to an inactive metabolite (M-1) *in vivo* by both carboxylesterase in the liver and pseudocholinesterase in the plasma.⁽⁴⁶⁾ Since the present study was conducted *in vitro* without any such enzymes, the radical scavenging activity of M-1 was not taken into account.

In conclusion, the present study demonstrated the direct scavenging activity of landiolol against multiple free radicals, which may contribute to its antioxidative and anti-inflammatory effects in addition to its clinical use as a selective β 1-blocker. Landiolol is a potential therapeutic agent in sepsis without hemodynamic complications. It could be used not only for preventing POAF but also for reducing risks of oxidative stress in the following stroke and heart attack.

Author Contributions

Study concept and design: SM; acquisition of data; OT, KO; analysis and interpretation of data: SM, OT, KO; drafting of the manuscript: SM, OT; critical revision of the manuscript for important intellectual content: YK, YO, CS, IY, TK; statistical analysis: OT; obtained funding: OT; administrative, technical, or material support: SM; study supervision: IY, TK.

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Abbreviations

AAPH	2,2'-azobis (2-amidinopropane) dihydrochloride
CABG	coronary artery bypass graft
carboxy-PTIO	2-(4-carboxyphenyl)-4,4,5,5-tetramethylimidazole-1-oxyl 3-oxide
CYPMPO	2-(5,5-dimethyl-2-oxo-2 λ 5-[1,3,2]dioxaphosphinan-2-yl)-2-methyl-3,4-dihydro-2H-pyrrole 1-oxide
DMPO	5,5-dimethyl-1-pyrroline-N-oxide
DPPH	2,2-diphenyl-1-picrylhydrazyl
ESR	electron spin resonance
IC_{50}	50% inhibitory concentration
ISO	isoproterenol
MDA	malondialdehyde
NOC7	N-methyl-3-(1-methyl-2-hydroxy-2-nitrosohydrazino)-1-propanamine
4-OH TEMP	4-hydroxy-2,2,6,6-tetramethylpiperidine
POAF	perioperative atrial fibrillation
ROS	reactive oxygen species
TBARS	thiobarbituric acid reactive substance
TEMPOL	4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl radical

Conflict of Interest

No potential conflicts of interest were disclosed.

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