ReviewArticle

AnesthesiaandPulmonaryHypertension:ANarrativeReview

Abstract

Pulmonary hypertension (PH) is a complex disease of the cardiopulmonary system. Perioperative management of PH is one of the mostchallenging issues for the anesthetists. Morbidity and mortality are significantly high in PH patients undergoing surgery due to right heartfailure, arrhythmia, atrial fibrillation, ischemia, hemodynamic unstability, hypoxia, respiratory failure, renal failure, sepsis, and stroke. InPH patients, it is important that more than one physician, including anesthesiologist, intensivist, pulmonologist, cardiologist, and surgeon,discuss the patient's possible difficulties and complications with a multidisciplinary approach and make a decision. In order to optimize themanagementofPHpatients,itisnecessarytocomprehensivelyevaluatetheunderlyingcause,pathophysiology,riskfactors,course,andtreatmentof the disease. A balanced anesthesia technique, including inhalation or intravenous agents, appropriate regional anesthesia (RA), opioids,and α-2-adrenoceptor agonists, may provide the most uniform hemodynamic profile in these patients. The basis of anesthesia managementshould(is)betopreventandtreattriggeringfactors,provideperfusionpressures,andoptimizerightventricularfunctions.Advancedmoni toring,pulmonaryvasodilatortherapies,adequateanesthesiaandanalgesia,andappropriateventilatorsettingsshouldbeperformedforpatientswithP H.PatientswithPHshouldbefollowedintheintensivecareunitinthefirst48–72hpostoperatively.Ourreviewaimstofocusonappropriatepreoperative preparation, perioperative monitoring, anesthesia and ventilator management, pain control, preventive methods, and treatmentinpatients withPHin light of the literature.

Keywords: Anesthesia management,comprehensivepreoperativeevaluation,multidisciplinaryapproach,pulmonaryhypertension

Introduction

Pulmonary hypertension (PH) is a heterogeneous systemicdisease that affects theheart, brain, liver, kidneys, gastrointestinal tract, skeletal muscles, endocrine, immuneand autonomic systems and it eventually leads to the rightventricular failure (RVF).[1,2] The pathophysiology includesdecreasedorganperfusion,unbalancedneurohormonal activation, oxidative stress, abnormal immune cell signaling,andvarioushemodynamicconsequencesinresponset otheinteractionofthesesystems.Themostcommoncausesof postoperative mortality in PH patients are acute RVF,arrhythmias (particularly atrial fibrillation [AF]), ischemia,congestiveheartfailure(CHF),unstablehemodynami cstatus,hypoxia,respiratoryandrenalfailure,sepsis,andstroke.[2 ,3]

PH is seen in 15–50 people per million.[4] Although it usuallyaffects women between the ages of 30 and 60, adverse clinicaloutcomesaremoreoftenpronouncedinmen.Hereditarya nd idiopathiccausesaccountfor52.6%ofallPHcases.Themostcom mon etiological causes are left heart or lung diseases.[4,5]Earlydiagnosisandtreatmentinpatientswith PHare criticalin(preventing)morbidity andmortality.[6]

PHisasevereprogressiveandchroniccardiopulmonarydiseasea ffectingpatients' clinicalcoursethroughouttheperi-operative period. Our review aims(is) to focus on how tomanage the patients with PH properly and effectively asanesthesiologists in the perioperative period.

DefinitionandClassification

Thediagnostic criteria for PHinclude:

a. Meanpulmonaryarterypressure(mPAP)>25mmHgatrest or

b. mPAP >30mmHgduringexercise
c. Pulmonary vascular resistance (PVR) >240 dyn/s/cm^5(N: 100–200).

PHisahemodynamicandphysiopathologicalconditioncharacterizedbyaprogressivecourse.AnmPAPbetween20 mmHgand 24 mmHg is defined as borderline PH.[2,7,8]PH is divided into five groups in terms of etiological causes,hemodynamic,andtherapeuticmodalities[Table1].[2,5,8]

1. Pulmonaryarterialhypertension(GroupI)
2. PHassociatedwithleftheartdisease(LHD)(GroupII)
3. PHduetochroniclungdiseaseand/orhypoxia(GroupIII)
4. PHduetopulmonaryarteryobstructions(GroupIV)
5. PHduetounclearand/ormultifactorialmechanisms(GroupV)

PHcanalsobedefinedaccordingtohemodynamicparameters[Table1].[8,9]

1. PrecapillaryPH:GroupsI,III,IV,andV
   - mPAP≥25mmHg
   - Pulmonaryarterywedgepressure(PAWP)≤15mmHg
   - PVR≥3woodunits(WUs).
2. IsolatedpostcapillaryPH:GroupsIIandV
   - mPAP≥25mmHg
   - PAWP>15mmHg
   - PVR≤3WU.
3. Combined precapillary and postcapillary PH: Groups II and V[8,9]
   - mPAP≥25mmHg
   - PAWP>15mmHg
   - PVR≥3WU.

Thefollow-upandtreatmentofPHintheperioperativeperiodareoneofthemostsignificantchallengesforanesthesiologists and intensivists due to high mortality andmorbidity.[6,10] By understanding the relevant and importantriskfactors,administeringappropriatetreatmentsbasedonPH classification,andenablingcarefulplanning;wecanaccuratelyand appropriately perform any surgery or intervention inthese patients. Management of patients with PH requires acomprehensive approach to optimize hemodynamics (rightventricular[RV],preload,afterload,andcontractility),minimizingrisksandtriggers,andcarefullyhandlingcomplications.[3,10,11]

Innoncardiacsurgery,mortalityandmorbidityvarybetween1%–18%and14%–42%,respectivelyforpatientswithPH.[3]Therefore,itsignificantlyprolongsthelengthofbothhospitaland intensive care unit (ICU) stays. Eventually, it causes anincreaseinhospitalcostsandtheriskofre-hospitalization.[2,3]

ThePathogenesisofPulmonaryHypertension

Etiologicalcausesthatinitiatethepathogenesisof PHincludeinappropriateangiogenesis,DNAdamage,geneticmutations,metabolic disorders, and factors that disrupt the vascularstructure.[12]Themediatorsmostaccusedinthepathogenesisof PH are endothelin 1, serotonin, thromboxane A_2 (TXA_2),epinephrine, norepinephrine (NE), nitric oxide (NO), andprostacyclin(PGI_2).Endothelin1isavasoconstrictorpeptide secreted by vascular endothelial cells, leading to pulmonaryvasoconstrictionandvascularsmoothmusclecellproliferation.NOandPGI_2areendogenousvasodilatorsproducedinpulmonary vascular endothelial cells, and their production isdecreasedin manytypes ofPH.[12-14]

ThepathogenesisofPHoccursinthreedifferentstagespathologically [Figure 1]: (1) endothelial dysfunction, (2)vascular remodeling, and (3) decreased apoptosis,neoadventitial excess cell proliferation, and thrombosis inpulmonaryarterioles.[14,15]Endothelialdysfunctionistheprimaryfactorinthepathogenesis of PH,andmanymolecularpathways havebeendescribed.Geneticsusceptibilityissignificant in the development of PH. In particular, the bonemorphogenetic protein receptor type II gene is thought toplayarolein75%offamilialcasesand20%ofsporadic

Table1:Classificationofpulmonaryhypertensiontypebasedonhemodynamicsandworldhealthorganizationclinicalgroups

Definition	Characteristic	WHOclinicalgroups
PH	mPAP>25mmHg	All
PrecapillaryPH	mPAP ≥25 mmHgPAWP ≤15 mmHgPVR≥3WU CO normal/reduced/high	PAH PH due to CLDCTEPH PHwithunclear and/ormultifactorialmechanisms
PostcapillaryPH	mPAP >25mmHgPAWP≥15mmHg CO normal/reduced/high	PHdue to LHD
IsolatedpostcapillaryPH	PAWP>15mmHg	PHdue to LHD
PostcapillaryPHwithprecapillarycomponent	DPAP-PAWP<7mmHg PAWP>15mmHgDPAP-PAWP≥7mmHg	PHdue to LHD

WHO=World health organization, mPAP=Mean pulmonary arterial pressure, PAH=Pulmonary arterial hypertension, PAWP=Pulmonary artery wedgepressure,PH=Pulmonaryhypertension,PVR=Pulmonaryvascularresistance,CTEPH=ChronicthromboembolicPH,CO=Cardiacoutput,DPAP=Diastolic PAP,CLD=Chroniclungdisease,LHD=Leftheartdisease,WU=Woodunits

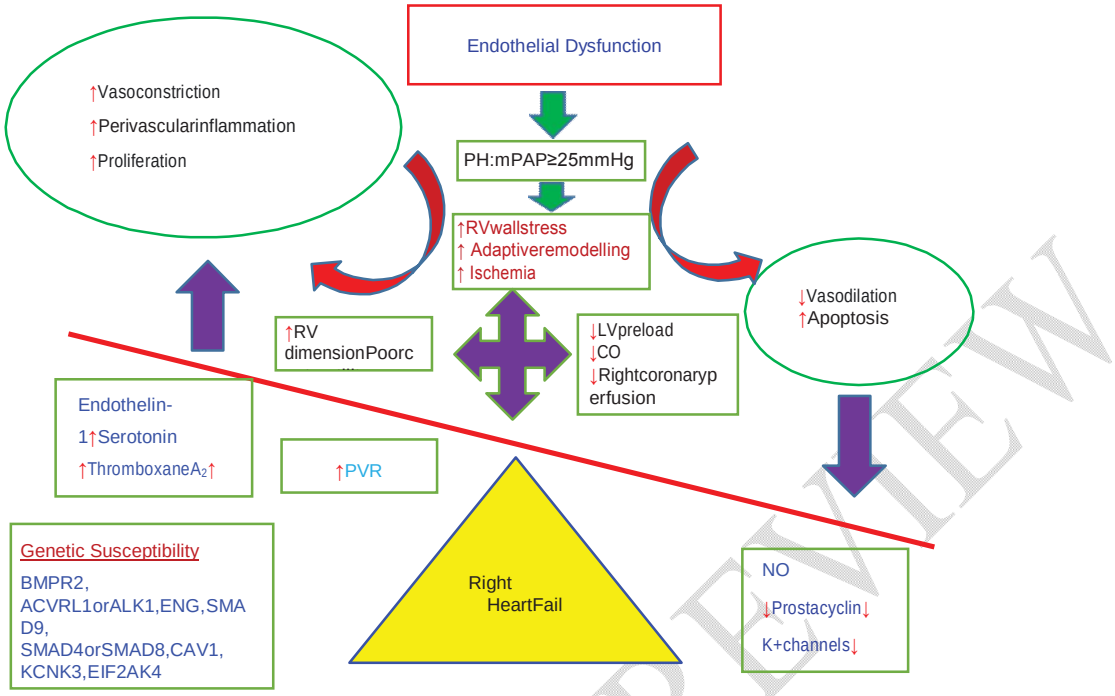

Figure1: Pathogenesisandgeneticsusceptibilityofpulmonaryhypertension.mPAP=Meanpulmonaryarterialpressure,PH=Pulmonaryhypertension,RV=Rightventricular,LV=Leftventricular,CO=Cardiacoutput,PVR=Pulmonaryvascularresistance,NO=Nitricoxide

cases.[16]Othermutationsassociatedwiththedevelopmentof PHincludeGDF2(codesBMP9),typeIreceptor(ACVRL1), andSMAD9(codesSmad8).Kchannelsubfamily Kmember 3 and caveolin-1 mutations have also been described, alongwith others.[14,16] Therefore, there is a relationship betweenvasoconstrictive and proliferative mediators (endothelin-1,serotonin,and TXA_2),whicharenormallyregulatedandbalancedaccordingtophysiologicalrequirements.ThisbalanceisdisturbedinPHamong mediatorswithvasodilatoryand anti-proliferative effects (NO, PGI_2, and K^+ channels ofsmooth muscle cells). PH develops due to increased activityofserotonin,endothelin-1,TXA_2mediatorsanddecreased activityofNO,PGI_2mediators,K^+ channelsofsmooth muscle cells.[14-17] Raised PVR caused by progressive vascularremodelingmayleadtoPHcrisisandRVF,thathasveryhighmorbidityandmortality[Figure 1].[18,19]

PerioperativeAnesthesticManagement

Preoperativeevaluation

The management of PH patients can be challenging andcomplicated. Detailed preoperative evaluation and correctanesthetic management will significantly increase the chancesofasuccessfulperi-operativeoutcomeinthesepatients.SincePHaffectsmanyorgan systems(heart,lungs,liver,and kidneys), surgical preparations should be guided by ateam's comprehensive anesthetic, surgical, pulmonary, andcardiacevaluation.Perioperativeplanningshouldbedonebyamultidisciplinaryteaminequippedcenters [Figure2].[1,10,11,20]

Detailed history, signs, symptoms, and physical examinationareextremelyimportantinthepreoperativeassessment.

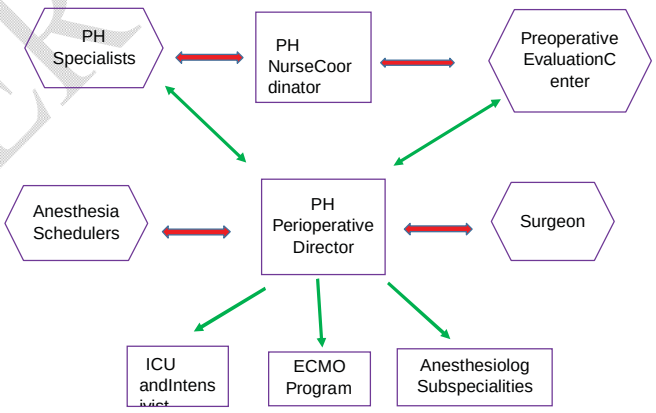

Figure 2: Management of pulmonary hypertension in the peri-operativeperiod.PH=Pulmonaryhypertension,ICU=Intensivecar eunit,ECMO=Extracorporealmembraneoxygenation

The preoperative evaluation of the patient with PH and theidentified risk factors are summarized in Figure 3.[6,10,11,20]. Allimportantfactorsshouldbeconsideredintheevaluation,such astheetiologyanddiseaseseverity,comorbidconditions,typean demergencyofthesurgery,thepatient'sfunctionalstatus,home medicationregimen,treatmentadherence,preoperativemedic ationoptimizationandappropriatetreatment,andassessmentof baselineoxygenrequirements.[6,20-22]Thepresenceof RVF findings such as S3 gallop, neck venous distention,peripheraledema,hepatomegaly,andabdominalasc itesinthephysicalexaminationareimportantforclinicalfollow-up.[23,25]

Ingeneral,theprimaryinvestigationsincludeacomprehensivem etabolicpanel,preoperativeroutinelaboratoryevaluations

(hemoglobin andhematocrit, creatinine, glomerularfiltration rate, pro-brain natriuretic peptide [pro-BNP], andliverfunctiontests),pulmonaryfunctiontestsinvolvingarterialbloodgas (ABG)analysis,chestradiography,anelectrocardiogram (ECG), transthoracic echocardiogram (TTE),6-min walk distance (6-MWD) test, should be obtained andreviewed when necessary.[6,10,21,22] There are identified riskfactors to determine the prognosis in terms of mortality andmorbidity[Table2].[3,6,10]

If the patient has dyspnea at rest, syncope history, functionalimpairment, presence of hypoxemia, exacarbated symptomsof RVF, or acid-based changes on the day of surgery, theanesthesiologistandsurgicalteamshouldconsidertherisk-benefit ratio if the operation is not urgent and confirmthat the anesthetist has the knowledge, attitude, and tools tomanagethisstatuswell,incaseofacuteRVFdevelopment.[10]Perioperativeriskfactorsincludeoperation-specificandpatient-related factors. The most important patient-relatedfactorsaretheNewYorkHeartAssociationgrade>2,6-MWD <300 m, estimated history of diagnosis, coronaryartery disease, RVF, chronic kidney disease, and pulmonarythromboembolism(PTE).[23,25]Surgicalfactorsincludeemergencysurgicalproceduresthatlastlongerthan3h,moderate or high-risk surgeries (including thoracic, majorabdominal,andorthopedicsurgeries),and proceduresthatmayincreasetheriskofvenousinsufficiencyorembolization,anduseofvasopressors.[3,10,26]Topredictpostoperativecardiacmortalityinnoncardiacsurgery,monitoringofpro-BNPlevelsisrecommended.[6]

It is common for patients with PH to overlook their diseasein the preoperative period, and TTE findings can often beunnoticedinthesepatients.Therefore,TTEshouldbeevaluated indetailinpatientswithsuspectedPH.Weshouldconsiderthatsystolic pulmonary artery pressure (sPAP) measurement canbebeneficialfortheriskstratificationandoptimalguidingfortheintraoperativemanagementofthesepatients.PatientswithsPAPabove35mmHgshouldbeevaluatedmorethoroughly.[23]Tricuspidannularplanesystolicexcursion(TAPSE)shouldbebetween 17 mm and 20 mm. TAPSE provides a great deal ofinformationaboutRVfunctionandprognosisinPH.Inaddition,rightatrialenlargementsurface(>27mm^2),TAPSE/sPAP(N: <0.19mm/mmHg),tricuspidregurgitationvelocity(TRV)(N: <2.8m/sn)measurementscanalsogiveinformationaboutheprognosis. The presence of pericardial effusion, decreasedTAPSE,increasedTAPSE/sPAP,TRV,andrightatrialenlargement surface (>27 mm^2) are distinguished prognosticmarkers.[22] Preoperative determination of prognostic factorsby TTE in patients with PH is vital for optimizing anestheticmanagement,preventingcomplications,anddecreasingmortalityandmorbidity[Table3].[23,24]

PatientsshouldbereassessedandoptimizedbeforeoperationtodecreasePVRandimproveRV functionifnecessary.In addition, transesophageal echocardiography (TEE) andpulmonary artery catheterization (PAC) should be evaluatedpreoperatively if the patient has comorbidities or symptoms ofRVF.[10-13,23]

Medications used for treating PH should be taken before theoperation. If the patient is not on treatment and the operationwill not be postponed, Sildenafil 0.5 mg/kg PO every 6 h,50–100mgdailyforadults,or0.2mg/kg/hintravenous(i.v.)shouldbe started.

Fluid restriction and diuretics should be considered in RVFandhypervolemia.Anti-coagulationisneededforthrombosis

Table2:Prognosticassessmentinpulmonaryhypertension

Prognostic determinant	Risk		
	Low	Intermediate	High
ClinicalsignsofRHF	Absent	Absent	Present
Progressionofsymptoms	No	Slow	Rapid
Syncope	No	Occasional	Repeated
Functionalclass	I, II	III	IV
6-MWD(m)	>440	165–440	<165
Cardiopulmonary exertion test	VO_2-peak>15mL/kg/min(>65%) VE/VCO_2<36%	VO_2-peak11–15mL/kg/min(35%–65%) VE/VCO_2(36%–44.9%)	VO_2-peak<11mL/kg/min(<35%)VE/VCO_2≥45%
BNPorNT-proBNP	BNP<50 ng/L NT-proBNP<300ng/L	% $ScvO_2$>70% PaO_2<80mmHg	BNP50–300 ng/L NT-proBNP300–1,400ng/L
Imaging techniques	RAarea<18 cm^2 Nopericardialeffusion		RAarea18–26cm^2 WithoutorwithminimalpericardialeffusionRAP8–14 mmHg
Hemodynamics	RAP <8 mmHgCI≥2.5L/min/m^2SvO_2>65		CI2.0–2.4L/min/m^2 $SvO_2$60%–65%

$ScvO_2$55%–70% $PaO_2$50–65mmHg	BNP>300 ng/L NT-proBNP >1,400 ng/LRA area >26 cm^2Pericardialeffusion RAP>14 mmHg CI<2.0L/min/m^2 SvO_2<60% $ScvO_2$<55% PaO_2<50mmHg

VE/VCO_2=TheratiobetweenminuteventilationandCO_2production,VO_2-peak=Peakoxygenuptake,RHF=Rightheartfailure,6-MWD=6-minwalkdistance test, BNP=Brain natriuretic peptide, CI=Cardiac index, NT-proBNP=N-terminal prohormone brain natriuretic peptide, RA=Right atrium,RAP=Rightatrium pressure,SvO_2=Oxygen saturationmixed venousblood, $ScvO_2$=Central venousoxygen saturation

prophylaxis.Besides,iftheriskofvenousthrombosisishighandt hereareclinicalsigns,heparinshouldbegivenasbridgetherapy instead of coumadin. Anemia and iron deficiencyshould be corrected in the preoperative period to preventworsening(of)PH.ACEI,ARBs,β-blockers,andivabradineshouldbe avoided in the preoperative period.[3,7,10,23] In our clinic,we start treatment to PH patients according to the etiologicalreason preoperatively (sildenafil, heparin, diuretic, etc.) andcontinue with appropriate medication (milrinone, inotropes,and diuretics) in the intraoperative period.

Intraoperativemonitoringandmanagement

Anesthesiaorsedationishighlyriskyin PHpatientswithorwithoutRVF.Operationgroupsaccordingtoriskratioare given in Table 4.[3,10] Since PH patients are difficult tomanage,hemodynamicinstabilityisquitecommon.Currently, anesthesiologistsareincreasinglylikelytoencounterPHpatients who apply for elective operations.[10,27] Understandingthe underlying cause, subgroup, and severity of PH allowsanesthesiologisttomakeacomprehensiveanesthesiamanagement plan to reduce patient-related risks. With theadventofadvancedhemodynamicmonitoringtechniquesand treatments, successful management of these patients isincreasing.[27]

Individualizedpreoperativeriskevaluation,treatmentoptimization,andadvancedperi-operativeplanningcanreducedifficulties and complications. To minimize complications,evidence-based,systematic,anddisciplinedteamconsensus isrequired. Anestheticandsurgicalstresscanexacerbate PH and lead to arrhythmias, CHF, myocardial infarction,postoperative respiratory failure, hemodynamic instability,anddelayedextubation.[23] Anesthesiologistsneedto provideoptimizinghemodynamics,ventilation,oxygenation,perfusion,maintaningbodytemperature,acid-base,andfluid-electrolytebalance, using therapeutic vasodilators or vasopressors whennecessary,(by)avoidingfactorsthatmaytriggerPH,andcontrollingpain peri-operatively to ensure better outcomes.

AnestheticapplicationsofPHareshowninTable5.[3,10,23]

Inthecaseofintravascularvolumedepletionduetoinsensiblelossesandexcessivebloodloss,theCOdecreasesbecauseofinsufficientright-sidedfillingpressures,andthereforeperfusioncannotbeachieved.[3]Ifnecessary,volumereplacement with appropriate fluids and inotropes should bestartedimmediately.Themaingoalofanestheticmanagement inPHpatientsshouldbetopreventRVF(,)andPHcrisesandtoprovidesystemicperfusion.[12]

PatientswithPHshouldbeappropriatelypremedicated,butadequatepreoxygenationshouldbeensured,especiallyinanesthesiainduction,andhypotensionandrespiratoryacidosistobeprevented asmuchaspossible.Invasivemonitoringshouldbeperformedin additiontostandardmonitoring,basedontheriskoftheoperation, duration,andconcomitant diseases. TheAmerican Society ofAnesthesiologistsrecommendsECG,noninvasiveheartrate, bloodpressure(BP)devices,pulseoximetry(SpO_2),

Table3:Peri-operativeriskassessmentaccordingtotransthoracicechocardiogram(systolicpulmonaryarterypressure,tricuspidannularplanesystolicexcursion/systolicpulmonaryarterypressureandtricuspidregurgitationvelocity)

RV/PAsystolicpressure(sPAP)	TAPSE/sPAP(mm/mmHg)	TRV(m/sn)	Secondarysigns of PH	ProbabilityofPH	SeverityofPH
<35 mmHg or undetectable	<0.19	≤2.8	No	Low	Mild
<35 mmHg or undetectable 35–50mmHg	0.19–0.32	2.9–3.4	Yes No	Intermediate	Moderate
35–50mmHg	>0.32	>3.4	Yes	High	Severe
>50 mmHg			Notrequired	High	

sPAP=Systolicpulmonaryarterypressure,TAPSE=Tricuspidannularplanesystolicexcursion,TRV=Tricuspidregurgitationvelocity,PH=Pulmonaryhypertension,RV=Rightventricular,PA=Pulmonaryartery

Table4:Typesofsurgeryaccordingtoriskstatusinpatientswithpulmonaryhypertension

Lowrisk:<1%	Intermediaterisk:1%–5%	Highrisk:>5%
Superficial surgeryBreast Dental Endocrine thyroidEyeReconstructive Carotid asymptomatic (CEA or CAS)Gynaecologicminor Orthopedic minor (meniscectomy)Urological minor (transurethralresection of the prostate)	Intraperitonealsplenectomy,hiatalherniarepairch olecystectomy CEAand CAS Peripheral arterial angioplastyEndovascular aneurysmEndovascular aneurysm repairHeadandneck surgery Neurologicalororthopedicmajor(hipandsupınesurgery)Urologicalor gynecological major Renal transplant Intra-thoracic nonmajor	Aorticandmajorvascularsurgery Open lower limb revascularisation or amputationThromboembolectomy Duodenal-pancreaticsurgeryLive resection Bile duct surgeryOesophajectomyAdrenalresection TotalrepairofaperforatedbowelTotal cystectomyPneumonectomy

Pulmonaryorlivertransplant

CEA=Carotidendarterectomy,CAS=Carotidarterystenting

Table5:Anestheticimplicationsofseverepulmonaryhypertension

Period	Anestheticimplication
Preoperative	A comprehensive evaluation of PH severityAvoidanxiety,painandsympatheticstimulationAvoidoversedationandhypoventilation ContinueallPH-specific,long-termtherapyperioperatively
Intraoperative	Usesuitableinvasivemonitoring Provide adequate anesthesia and analgesiaPPVparameters FiO_2 titrate to 60%–100%Low tidal volumes (6 mL/kg)$PaCO_2$:30–35 mmHg $EtCO_2$:30–35mmHgLowPEEP(5–10cmH_2O) Aggressively treat hypotensionMaintainsinusrhtymiMaintainsystemicpressures OptimizeRVfunctionandCOwithadequatepreload,SVRand contractility MAP>65mmHg,CI≥2.2L/min/m^2M onitor RV and treat dysfunctionOptimizefluidbalance Minimize blood lossMinimizetransfusion AvoidtriggerfactorsthatworsenPHandincreasePVR:Hypoxemia HypercarbiaAcidosisHypothermiaHypervolemia Increased intrathoracic pressureAtelectasis and hyperinflationPain ConsiderpulmonaryvasodilatorstodecreaseRVafterload
Postoperative	Avoidpainandshivering Advancedmonitoring Closely follow up first 48–72 h in the ICU

PH=Pulmonary hypertension, PPV=Positive pressure ventilation, FiO_2=Fractionofinspiredoxygen, $PaCO_2$=Partialpressure ofCO_2, $EtCO_2$=End-tidalCO_2, PEEP=Positiveend-expiratorypressure, RV=Rightventricular, MAP=Meanarterialpressure, CO=Cardiacoutput, CI=Cardiac index, PVR=Pulmonary vascular resistance, SVR=Systemicvascular resistance, ICU=Intensive care unit

respiratoryrate(RR),end-tidalcarbondioxide($EtCO_2$),and temperature monitoring for all surgical cases. Cardiacoutput (CO) monitoring with advanced dynamic parametersmayguide thehemodynamic management inmajorsurgeries. Neuromuscular monitoring should be performedwithbispectralindex(BIS)andtrain-of-fourmonitoring.While standard monitoring is considered adequate for minorand moderate operations in functional status II, all majoroperations and procedures in functional status III should beperformed with advanced monitoring.

Warm fluids are ofchoicetopreventhypothermiaandi.v.liquidheaters,heatingblankets,andforcedairheatersshouldbeused.[3,10,11,23]

Intermittent ABG sampling should also be performed. Anarterial line may be placed to provide continuous access toABG samples and systemic BP monitoring. It allows rapidintervention, appropriate ventilation management, and drugtreatment determination.[28-30] Central venous catheterizationshouldbeperformedcarefullytopreventtriggering arrythmias.Central venous pressure (CVP) can be monitored for volumestatus. CO monitoring includes the following hemodynamicparameters:

- Systemicvascularresistance(SVR)
- Strokevolume
- Pulsepressurevariation
- Strokevolumevariation
- Extravascularlungwater
- Cardiacindex(CI)
- Centralvenous oxygensaturation($ScvO_2$)
- Mixedvenousoxygensaturation(SvO_2).

TEEmustbekeptintheoperatingroomintraoperatively.PACcan beplacedandevaluatedpreoperativelyinseverePHcaseswhen necessary.[10,30-32] The main goal in perioperative targetedtherapyshouldbetoensuretheperfusionandoxygenation ofvital organs.[33] In addition, its monitoring can show globaltissue perfusion.[30] In our clinic, we perform PAC in PHpatients undergoing major surgery and support it with TEE.TEEcangiveinformationoncardiacwallmotions,anatomy,valves'functions,andevaluatevolumestatus.[10,34-36]

AnestheticTechniquePreferenceandMethods

Currently, no evidence-based information is available forchoosinggeneral,regional,orcombinedanesthesiaasanesthetictechniqueforPHpatients.Generalanesthesia(GA)isfrequentlyusedinpatientswithPH.However,currentPH guidelines and experts recommend regional anethesia(RA) in eligible patients for elective surgeries, as positivepressure ventilation (PPV) with high positive end-expiratorypressure (PEEP) and tidal volume may worsen RV afterloadand, thus, PH clinic. Spinal anesthesia should be avoided asmuch as possible due to its sympathetic-blocking effects andrapid onset.[10] Many opinions suggest a balanced method withhigh-doseopioidsandlow-doseinhaledanestheticsifGAistobeapplied.[10,11]Itisvitaltomaintain RVfunctionandreduceriskfactorsthatcausepulmonaryvasoconstriction(increasing RVafterload)orsystemichypotension(reducingRVperfusion).[36] Epidural and/or peripheral nerve blocks areuseful in peri-operative pain control. Uncontrolled pain maytrigger PH. Therefore, it is important to make a personalizedplan according to the underlying etiology, pathophysiology,andsystemicinvolvementinapatientwithPH.[10-12]

TheadvantagesofGA allowcontrolledventilation,safeoxygenation,uncomplicated airway,andadirectrouteforadministeringinhaledpulmonaryvasodilators.ThedisadvantagesofGAareduetoPPV,PEEP,andtheBPchangescausedbyanesthetics.Severehypotensionmaydecreasecoronaryperfusionpressure(CPP),resultinginaviciouscircle

thatmayleadtoRVischemia,disruptionofRVcontractility,cardiogenicshock,andeven death.[37]

SufficientdepthofanesthesiaandanalgesiaprovidereducingcatecholaminedischargeandPVR.Laryngoscopyandintubation can cause PH crisis, RVF, and death in patientswithseriousPH;thus,meticulouslylaryngoscopyandintubationmethodsareessential.Lidocaine,opioid,Mg^{++}, α-2agonists,andnonhistamine-releasingnondepolarizing muscle relaxants can reduce the sympathetic response andsuppress the stress response to intubation.[10] Moreover, i.v. ornebulized treatments with inhaled NO (iNO) or prostanoidsmay be given to minimize PH responses to intubation. Theoverall goal should be to prevent changes in preload, SVR,andcontractionofRVtomaintainCO.[38]

BeforeinductionofGA,apatientwithPHmustbeadequatelypreoxygenatedwith100%fractionatedinspiredoxygen(FiO_2)topreventhypercarbia,respiratoryacidosis,hypoxemia,andtoincreasefunctionalresidualcapacity.Oxygenisapulmonaryvasodilator and helps prevent hypoxemia. Triggering factorssuch as hypoxemia, hypercapnia, acidosis, hypotension, andhypothermia should be avoided, and appropriate ventilation,adequate fluid therapy, and low-dose vasopressor should beadministeredwhenneeded[Table5].[3,26,39-41]

There is no ideal anesthetic agent for PH patients. Afterpremedicationwithbenzodiazepines,balancedanesthesia inductionandmaintenancecanbeachievedwithconcomitantuseofopioids,etomidate,propofol,ketamine,α-2agonists (dexmedetomidine and clonidine), and/or volatileanesthetics(suchasisofluraneandsevoflurane),asappropriate.[37]

Benzodiazepines, which cause minor respiratory depressionandhemodynamicchanges,canbeusedcarefullyin unstableconditions.Hemodynamiceffectsofinhalationalor i.v. anesthetics are given in Table 6. Propofol does notincrease systemic vasoconstriction with minimal pulmonaryvasodilation.[27]PropofolsignificantlyreducesSVR andslightly reduces cardiac contractility.[38] Therefore, propofolmaytriggeroxygendesaturationinpatientswithcardiacshuntandhighPVRbyacceleratingtheright-to-leftshunt.Therefore,

Table6:Effectofanaestheticagents

AnaestheticagentRVcontractility		PVR	SVR
Isoflurane	↓↓	↑	↓
Desflurane	↓↓	↑	↓
Sevoflurane	↓↓	↔	↓
NO	↓	↑↑	↑↑
Thiopental	↓	↔	↓
Etomidate	-	-	↔
Ketamine	↓	↑ adult, ↔ child	↑
Propofol	↓↓	↓	↓↓
Opioids	↔	↔	↓
Dexmedetomidine	↔	↔	↑

↓↓=Markeddecrease,↑↑=Markedincrease,↑=Increase,↓=Decrease, ↔=Nochange,-=Notknown.RV=Rightventricular,PVR=Pulmonaryvascularresistance,SVR=Systemicvascularresistance,NO=Nitrousoxide

careshouldbetakenininduction.[38]Althoughthiopentalhasno effect on PVR, it decreases RV contractility and causesmyocardialdepression andhypotension.[23]

Etomidateisawidelyrecommendedinductionagentbecause ofitsrapidonsetandhemodynamicstabilitywith minor effects on myocardial contractility, SVR, andPVR.[23,38] Ketamine-induced catecholamine release may causepulmonaryvasoconstriction,andthiseffectcanbeattenuat edwith pulmonary vasodilators, benzodiazepines, or increasingFiO .[37] Ketamine preserves SVR and BP without causingexcessive PVR, thereby protecting systemic and pulmonarycirculation. In addition, low doses of ketamine as part of themultimodalanalgesiamaybebeneficialforpaincontrol.[23,42]

Opioids have a modest impact on PVR and can be used toblunt response to sympathetic stimulation.[23,37,42] Short-actingopioids,includingremifentanil,arehighlyrecommended anesthetic drugs in balanced anesthesia.[23,42,43] Neuromuscularagents such as atracurium and mivacurium that can increasePVRbyreleasinghistamineshouldbeavoidedinpatient swithPH. Rocuronium and vecuronium are generally preferred asneuromuscularblockers.[23,43]

Dexmedetomidineisacentrallyactingα-2agonistthatpreventstheincreaseinPVRbyreducingthestressa ndhemodynamicresponse to intubation and extubation with its sympatholyticeffect.Dexmedetomidineisaconvenientandeff ectivesedative-anestheticdrugforreducingopioidusageinbothGAand RA. It is an important advantage that dexmedetomidinedoesnotinteractwithdiureticsandphosphodi esterase(PDE)-5inhibitorsused inthe treatment ofPH.[44]

Volatileanestheticsreducehypoxicpulmonaryvasoconstriction(HPV),thusdecreasingventilation-perfusion(V/Q)matching.[45]Volatileanestheticagentscanbead ministeredwithoutadverseeffects on PVR. Minimum alveolar concentration values ofbelow1.0aregenerallyrecommendedtominimizemyocardial depression. BIS monitoring can be helpful to evaluate theanesthetic depth.[46] All inhalation anesthetics reduce SVR byblockingATP-dependentK^+channels,causingvascularsmoothmuscle relaxation and eventually hypotension. Nitrous oxideshouldnotbeusedduetoincreasesinPVR.[23,38,42,43]Desflura neincreasesHPV,whileisofluranereducestheseverityofHPV.I soflurane and desflurane may reduce RV contractility in adose-dependentmannerwithariseinRVafterload.[46]

Isoflurane and enflurane cause pulmonary vasodilation andinhibitionofendothelium-dependentrelaxationwithoutprominent change in pulmonary circulation tonus. SevofluranecausesadecreaseinRVfunctionandhasapulmonar yvasodilation effect similar to isoflurane, which does not affectPVR.InPHpatients,sevofluraneandisofluranearegeneral lypreferredforinductionandmaintenanceofanesthesia.[45]

Extubation should be performed in patients with FiO_2 below40%andappropriateventilationparameters.Inaddition,d eeporearlyextubationshouldbepreferredtopreventsympathetic stimulationinthesepatients.[23,42,43]

As a result, a balanced anesthesia with opioids and low-dosevolatileanestheticagentsisusedformaintenance.Maintaining thebalancebetweenoxygendeliveryandconsumptionduringanesthesiaandsurgeryisimportant.[23,38,42] Inourclinic, etomidate and opioids are mostly used for anesthesiainduction.Weuseremifentanilordexmedetomidine, volatileagents (sevoflurane), neuromuscular blockers (rocuroniumandvecuronium)foranesthesiamaintenanceinthespatients.We also use dexmedetomidine for anesthesia and sedation inpatientswhohave epidural anesthesia.

RA techniques can help maintain spontaneous breathing andavoidhighpulmonaryarterypressure(PAP)andintrathoracic pressure caused by PPV.[38] Plexus blockades and peripheralnerveblocksareadvantageousastheyminimallyaffecthemodynamics,andhaveahighsuccessrateandbetterpostoperativepaincontrol.ContinuousRAmethodsaresignificant utilities for both intraoperative anesthesia andpostoperativeanalgesia.Whenadministeringepiduralanalgesia,theconcentration,dose,andvolumeofdrugsshouldbe fractionated and administered carefully, as they causeSVR, CPP reduction, and RVF.[38,39] In thoracic and abdominalsurgery, the combined administration of GA and thoracicepiduralanesthesia(TEA)isrecommendedtodecreasethe utilization of GA anesthetics and peri-operative opioidconsumption.TEAhasnoadverseeffectonoxygenationandPVR.[39,40]However,high-levelepiduralblock(T–T)may causeasympatheticblockadethatalterscardiacinotropyandchronotropy.Epiduralanesthesiaandanalgesiainpatients withPHareassociatedwithreducedarrhythmias,improved CO,betterpaincontrol,andreducedpostoperativeileus.

ManagementofPulmonaryHypertensiveCrisis

Factors suchashypotension, hypoxia, hypovolemia,hypervolemia,hypercarbia,respiratoryormetabolicacidosis,hypothermia,raisedintrathoracicpressure,andpainmaycause major cardiopulmonary complications by increasingPVR.[3,10,23,38,47] In a PH crisis (e.g., increased PVR and PAPintraoperatively), the most critical point is to avoid increasesin RV afterload and PVR. Maintaining RV contractility iscrucial.SincecalciumchannelblockersreduceSVR,CO,andCPP, they may cause ischemia in PH crisis. DecompensatedRVF,cardiogenicshock,andevendeathmayoccurduetoPHcrisis.[47]Hypothermiashouldbeavoidedasmuchaspossiblesinceitincreases SVR, V/Qmismatch,HPV,shivering,energyconsumption,andultimatelyPAPtoasignificantextent.Itis essential to maintain ventilation, oxygenation, systemicperfusion,andhemodynamics[Table5].[10,28,30]

ManagementofHypotension

Sudden hypotension should be avoided during scenario.[1,3,38] Severe hypotension can worsen RV function intwo ways: reducing CPP and ventricular interdependence.[47,48]Asaresult,perfusiondeterioratesgradually andoftenmanifestsascardiogenicshocktogetherwithischemicevents.[3,10,23,47,48]

TTE or TEE is the gold standard in diagnosing and guidingtreatmentapproachesinPHpatientswithhypotensionbecauseit provides detailed information about cardiac function andvolume status.[35] Since these patients have poor tolerance tosystemichypotension,theyshouldbetreatedwithappropriateinotropesand/orvasopressorssuchasNE,vasopressin,phenylephrine,anddobutamine.TreatmentwithiNO,asynthetic analog of PGI_2, or inhaled vasodilators such asiloprost may be beneficial to prevent exacerbations. It doesrestoresystemicBPandCPP.[48]Thehemodynamiceffectsofdrugsused in PH are given in Table 7.[48-54]

Vasopressin is a noncatecholamine agent that effectivelyrestores SVR without increasing PVR, RV afterload, andtachyarrhythmias.[49]Sincevasopressininducescoronaryvasoconstrictionathighdoses(>0.08U/min),thedoseshouldbe kept within a narrow range (0.01–0.08 U/min). Manyauthors recommend vasopressin as the first agent to increasecontractilityandSVR,andtopreventhypotensionforpatients withPHingeneralandnoncardiacsurgery.[49,50]

Pureα-agonistsshouldnotbegiventopreventhypotensionduetotheirnegativeeffectsonthepulmonarycirculation.NEisusually preferredtophenylephrineinthesepatients.[51,52]Dobutamineisasynthetic β-and β (β_1 β_2)-agonistwithmildperipheralα-agonists anesthesiainduction.IntermittentPPVmayalsoaffectRVpreloadandhavedeleteriouseffects.[10]

RVFisthemostseriousintraoperative complication in patients with PH. Preventingsystemichypotensioniscriticalperi-operativelyinthis

activity.ItprotectsSVRatlowerandintermediatedosesprimarilyb y its chronotropic effect. It improves CO and reduces PVR.Sincedobutaminealsoproducessystemicvasodilation,it willpotentiate systemic vasodilation effect of anesthetics. Thus,NEhavinginotropicandvasopressorpropertiesismoreof tenpreferred intraoperatively.[53,54] In our clinic, we use NE orvasopressinasthefirstchoiceincaseofsystemichypotension.

Table7:Drug'seffectsonhemodynamicparameters

	CI	PVR	SVR	PVR/SVR	TSG
Inotropes					
Epinephrine	↑↑	↑	↑↑	↓	↑
Dobutamine	↑↑	↓	↓	↓	↓
Isoproterenol	↑	←	←	←	←
Dopamine*	↑↑	←/↑	↑	↑	←/↑
Inodilators					
Milrinone	↑↑	↓↓	↓↓	↓	↓↓
Levosimendan	↑↑	↓↓	↓↓	←/↓↓	↓↓
Vasopressors					
NE	↑	↑	↑	↑	←
Phenylephrine	↓	↑↑	↑↑	↑	←
Vasopressin	↓		↑↑	↓	←/↑
IVprostanoids					
PGI_2(epoprostenol/flolan)	←	↓	↓	↓	↓

↑=Increased, ↓=Decreased, ←=No change, CI=Cardiac index,PVR=Pulmonaryvascularresistance,SVR=Systemicvascularresistanc e,TSG=Transeptalgradient,PGI_2=Prostacyclin,NE=Norepinephrine

WeuseiNO,sildenafil,andmilrinonefrequentlyinourclinicinaddition tothesetreatmentswhennecessary.Extracorporealmembraneoxygenation(ECMO)cancontributecardiopulmonary support when acute RVF is refractory tomedical therapy in the appropriate indication and clinical condition.[37,48,55]

ManagementofArrhythmias

Althoughventriculararrhythmiasareinfrequent,atrialflutter and AF are more common and can lead to right heartdecompensation.Inaddition,theserhythmdisturbancesimpairmyocardialoxygenation,resulting(in)decreasedRVcompliance and diastolic dysfunction. As a result, systemic hypotensionand RV ischemia may develop, worsening decompensation.Establishing and maintaining sinus rhythm in patients withParkinson's disease is extremely important. The aim shouldbetorapidlyprovidenormalsinusrhythmwithcardioversion,ablation,oramiodaroneinthepreoperativeperiod.[55]Incases where cardioversion or ablation are not suitable; calciumchannelblockers,β-blockers,andamiodaroneshouldbeconsideredin the preoperativeperiod.[47]

Weinsistonmaintainingnormalsinusrhythmperioperativelywhenever possible. We use amiodarone as the first agent forintraoperative arrhythmias. According to the patient's clinic,wealso use β-blockers or calcium channel blockers.

FluidManagement

Maintaining an optimal intravascular volume status in PHpatients is important and difficult. Relative or true hypovolemiamaydevelopwhencontinuousfluid-bloodlossesarecombinedwith the inflammatory response and prolonged losses to thethirdspacefrommajorsurgery.Insuchsurgeries,replacements hould be done with appropriate fluids to ensure effectiveintravascularvolume.[47,48]

Since RV dysfunction is present in most of the PH cases, fluidoverload and development of RVF have to be considered.Thesemaybedifficulttodetectclinically.Sincelarge volumes of fluid infusion can cause RVF due to existing RVdysfunctionand,indirectly,leftventricular(LV)dysfunction.FluidsshouldbegivenbyanalyzingdynamicparameterswithCO monitoring. Cold liquids should be avoided as much aspossible, as they may cause RV oxygen supply-consumptionimbalance.[3,23,47,55] In major surgeries, patients with RVFpoorly tolerate pericardial-pleural effusions due to excessivefluid shifts and blood loss impairing systemic perfusion andpressures.Thus,majorsurgeriesresultinincreasedmortality andmorbidityin thesepopulation.[22,23]

DrugManagement

Vasodilator drugs frequently used inPHare iNO,prostanoids,PDE-3–5inhibitors,andendothelinreceptorantagonists (ERA).[47] The effects and doses of vasodilatordrugsaregiveninTable8.[47,48,54-57]Theaimoftreatmentin

PH is to reduce RV afterload and PVR. Inhaled pulmonaryvasodilators are the most effective, accurate, and safe methodsofrestoring cardiac functions in PH.

- iNO(5–40 ppm continuously)
- InhaledPGI_2(nebulizedori.v.2–20μg/kg/min)
- Iloprost(5–10mg,inhaledover10min,every2–4hor i.v.1–3ng/kg/min)
- Milrinone(25–50μg/kgbolus,0.5–0.75μg/kg/mininfusion)
- Sildenafil(0.25–0.5mg/kg,every4–8hperoral,ori.v. 1.6mg/kg/day)
- Nitroglycerine(i.v.2–10μg/kg/min)
- Sodiumnitroprusside(0.2–0.3μg/kg/min)
- Epoprostenol(10–50ng/kg/mincontinuously).[48,54-57]

However, inhaled pulmonary vasodilator therapies have noeffectonthechronicthromboembolicPHsubtype.[56,57]

InthetreatmentofPH,iNOiswidelyusedinallperiods.[37]iNOdilatespulmonaryvascularsmoothmusclebyactivatingcyclicguanosine monophosphate (cGMP). Since iNO is rapidlyinactivated by hemoglobin, it has no systemic vasodilatoreffect. iNO causes pulmonary vasodilation, reducing PVR, RVafterload, and PAP without affecting SVR.[48] Since iNO onlyreaches the alveoli involved in gas exchange, it improves theventilation/perfusion balance by increasing pulmonary bloodflowintheseareas.[58-60]Inaddition,iNOsignificantlyimproves$ScvO_2$ and CO in critically ill patients with circulatory shocksecondarytoRVF.[60,61]However,itseffectsareshort-termasit is rapidly degraded by cGMP-PDE. Prostacyclin causespulmonaryvasodilationbyactivatingcyclicadenosinemonophosphate.[60] The effects of inhaled epoprostenol onhemodynamics and V/Q adjustment are similar to those ofiNO. Furthermore, prostacyclins inhibit platelet aggregationwithvasodilatoryeffects.Pulmonaryvasodilators shouldbe used with caution in PH subtypes caused by pulmonaryvenous-occlusivedisease,pulmonaryveinstenosis,andLHD,astheiruse beforetheobstructionisresolvedcanleadtoacute,life-threateningfataloutcomes.[59]Systemicvasodilatorscause a significant decrease in RV perfusion pressure byvasodilating the pulmonary and systemic vasculature. ERAsproduce vasodilation by antagonizing endothelin. Besides,theyhaveanti-inflammatoryeffectsandtheyreducevascularsmoothmuscleproliferation.[58] Thesedrugsareeffectivein improving hemodynamics and exercise capacity. In ourclinic, ERAs(Endothelial receptor antagonists) and PDE-5 inhibitors are prescribed orally bythe cardiologists in the preoperative period in these patients.Sinceinhaledpulmonaryvasodilatorsmaycauserebound PH and RVF, dose adjustment and discontinuation should bemadecarefully.[60,61]

MilrinoneisaPDE-3inhibitorwithinodilatorpropertiesthatimproveLVandRVcontractility,COanditcausesperipheralandpulmonaryvasodilation.Co-administrationofinotropicand/orvasopressorsmayberequiredtoprovideadequatemeanarterialpressure (MAP).[37,48] Drugs used to provide hemodynamicstabilityduringanesthesiaforpatientswithPHare givenin

Table8:Drugsusedinthetreatmentofpulmonaryhypertension

	Mechanism	Treatmentdose	Adverseeffects
Prostanoid			
Epoprostenol	Pulmonaryvasodilation	IV:1–2μg/hincreaseastoleratedwithinitialtarget6 mL/h after 48–72 h Nebulized:0.2–0.3mL/minof10–20μg/mL	Systemic hypotension, flushing,headache,diarrhoea,legandjawpain
Iloprost	Pulmonaryvasodilation	IV:1–2ng/kg/minincreaseastoleratedwithinitialtarget10 ng/kg/min after 48–72 h Nebulized5–10μgfor10–15min	Systemic hypotension, flushing,headache,diarrhoea,legandjawpain
NO pathwayNO	Pulmonaryvasodilation	Nebulized5–80ppmcontinuously	ReboundPH,methemoglobinemia
Inotropes			
Dobutamine	CI ↑↑PVR↓	IV:2.5–20μg/kg/min	Tachycardia HypotensionTachyarrythmias
Dopamine	CI ↑↑PVR ←/↑SVR ↑	IV:3–10μg/kg/min	Tachycardia HypotensionTachyarrythmias
Inodilators			
Milrinone	CI ↑↑PVR ↓↓SVR ↓↓	IV:50μg/kgover10min,then0.375–0.75μg/kg/min Nebulized:0.2–0.3mL/min	Hypotension
Levosimendan	CI ↑↑PVR ↓↓SVR ↓↓	6–12 μg/kg/min over 10 min, then 0.1 μg/kg/mininfusion	Hypotension
Vasopressors			
NE	CI↑PVR↑SVR ↑	IV:0.01–0.4μg/kg/min	Bradycardia
Phenylephrine	CI↓PVR ↑↑SVR↑↑	IV:40–100μgbolus,50–300μg/min	Bradycardia
Vasopressin	CI↓SVR ↑↑	IV:0.001–0.004U/min	Bradycardia

↑=Increased, ↓=Decreased, ←=No change. CI=Cardiac index, PVR=Pulmonary vascular resistance, SVR=Systemic vascular resistance, IV=Intravenous,NO=Nitricoxide, NE=Norepinephrine

Table8.Vasopressinhasminimalpulmonaryvasoconstrictiveeffects.Concomitantuseofmilrinoneandvasopressininthe intraoperative period is appropriate for preserving RVcontractility,SVR,andreducingPVR.[48,62]Dobutaminecanbeusedtogetherwithmilrinonebecauseitreduces PVR.[37]

In our clinic, we continue i.v. pulmonary vasodilator therapyintheintraoperativeperiod.Inadditiontothistreatment, we use iNO and milrinone with NE or vasopressin. Inhaledpulmonaryvasodilatorsmaybeadministeredthroughahigh-flownasalcannula,whichmayfacilitateweaningand extubation.[63,64] Oral sildenafil and tadalafil of PDE-5inhibitorspotentiatetheeffectofinhaledpulmonaryvasodilators.[48]Theyareeffectiveinalltypesof PH,including LHD.[65] Unlike other systemic vasodilators, theydonotworsenintrapulmonaryshuntinchronicrespiratory diseases.[48,65-67]PDE-5inhibitorsshouldbetitratedslowlyastheymaycausesystemichypotensionintheperi-operative period. Thegeneralopinionistobeginsildenafil10mg3 times daily and rise it to 20 mg as tolerated. For and oral sildenafil with milrinone infusion postoperativelywhennecessary.Inotropicsareoftennecessarytorestore RVsystolicfunction.[48]

Despite all interventions, patients with severe PH may notimprove their RV dysfunction and cardiogenic shock withseveredeteriorationoforganperfusionmayoccur.Maintainingsystemic perfusion is the most critical goal. The most effectiveand fastest way is to initiate veno-arterial (VA)-ECMO.[55]

Itcontributestotheimprovementofoxygenationandventilation,significantlyreducingPVR.[68]Thismayallowtimetosupplementothertherapieswithrespiratoryandcardiacsupports.Furthermore,itisusedasabridgetotransplantationin more critical situations.[69] We use VA-ECMO to preventRVFandassistcirculationwhennecessary.

Ventilationand Oxygenation Strategy

recentlydiagnosedpatients,sildenafilcanbestartedpreoperatively toprevent exacerbations of PH.[59] In our practice, we start oralsildenafilthreetimesdaily(for)7daysuntilsurgery,ifthesurgeryiselective,inthosediagnosedwithPHinpreoperativeperiod. Wecontinuemilrinoneinfusionintraoperatively

Theoptimizationofventilationandoxygenationisbasedon surgery type and anesthesia strategy. PPV worsens CO,[70]especially in the failing RV.[71] For adequate oxygenation,highFiO_2 (0.6–1.0)istypicallyusedtopreventhypoxicvasoconstriction.Itisappropriatetostartwithatidalvolumeof6mL/kgandnottoincreasethepeakairwaypressuresabove30mmHg.[10]Alveolaroverstrainshouldbeavoidedtoprevent

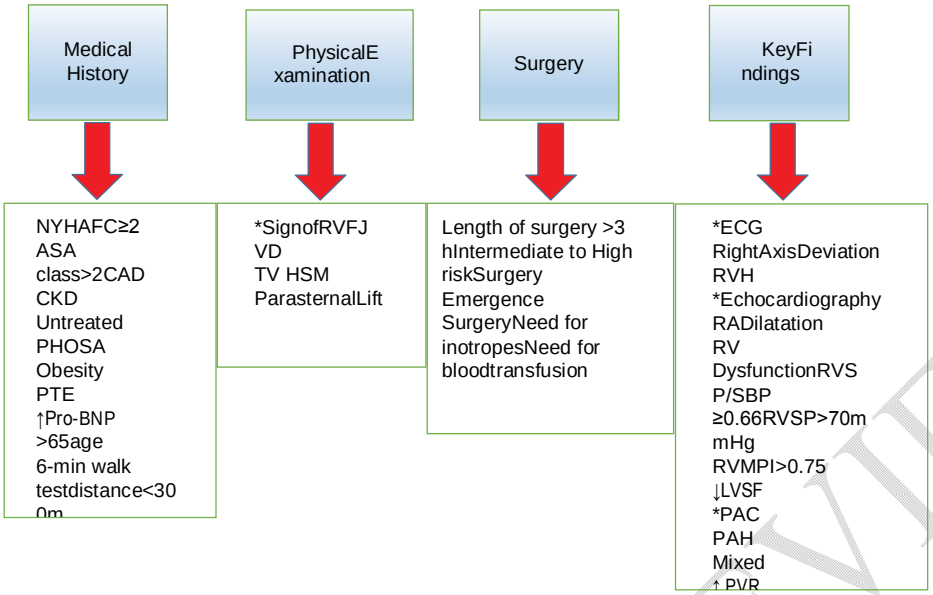

Figure 3: Preoperative evaluation of the patient with pulmonary hypertension and identified risk factors. ASA=American society of anesthesiologist,CAD=Coronary artery disease, CKD=Chronic kidney disease, PCWP=Pulmonary capillary wedge pressure, JVD=Jugular venous distension, LVSF=Leftventricular systolic function, NYHA FC=New York Heart Association Functional Classification, OSA=Obstructive sleep apnea, PAH=Pulmonary arterialhypertension, PTE=Pulmonary thromboembolism, PH=Pulmonary hypertension, PVR=Pulmonary vascular resistance, RA=Right atrium, RVF=Rightventricular failure, RVH=Right ventricular hypertrophy, RVMPI=Right ventricular myocardial performance index, RVSP=Right ventricular systolicpressure,SBP=Systolicbloodpressure,TVHSM=Tricuspidvalveholosystolicmurmur,ECG=Electrocardiographic,*=Indicatesthepresenceofhighriskinpatients

theincreaseinPVR.TheRRshouldbeadjustedtotarget$PaCO_2$of30–35mmHgand$EtCO_2$of30–35mmHg.Sincehypercarbiaand acidosis can increase pulmonary vasoconstriction andworsenPH,adequateminuteventilationshouldbeprovided.[10,23]PEEP is set to 5–10 cm$_2$H O, ideally.[23] Adequate PEEP andrecruitmentmaneuversmaycontributetothemaintenanceof V/Q matching. Higher PEEP levels can reduce preload andcause systemic hypotension. It may be required to increaseFiO_2 rather than PEEP to improve oxygenation. In thoracicsurgery, one-lung ventilation is avoided as much as possiblebecause blood flow to the nonventilated lung decreases andthe ventilation/perfusion ratio deteriorates, resulting in acuteexacerbationofHPV-relatedPH.[10]

In laparoscopic surgeries, pneumoperitoneum with insufflationreduces lung compliance and venous return due to increasedintraabdominalpressureleadingtothedeteriorationof oxygenationandhemodynamics.Inaddition,increasedintraabdominalpressureandhypercarbiamaytriggerexistingPHandleadtosignificantcomplications.[10]Therefore,closeandcarefulmonitoringisrecommendedtoensuremPAP <35, PVR/SVR ratio <0.5, MAP >65 mmHg, systolicpressure>90mmHg,andCI>2.2L/min/m^2.[3,10,23,48]

ANESTHESIAFORPREGNANTSWITHPULMONARYHYPERTENSION

Changesoccurinvitalorgansduetophysiological,mechanical,and hormonaleffectsduringpregnancy.Theseeffects,inturn,areduet o:(1)constrict(constriction)ofthenearbyorgansbyenlargement

oftheuterus,(2)incrementofrelaxinpeptide,whichmediatethevasodilatoryeffectsofhormonalchangesbyestrogenandprogesterone and facilitate blood flow to critical organs, (3)increases in the systemic circulation. PH makes significantchangesinallsystems(cardiovascular,respiratory,andhematologic)ofpregnantwoman.[72]InpregnantwithPH,the outcome is not good despite advanced treatments. Avoidingpregnancy as possible for these patients is recommended.Epoprostenol, treprostinil, nebulized iloprost, sildenafil, andiNOcanbeusedinmedicaltreatment.ERAsarecontraindicatedduringpregnancyduetotheirteratogeniceffects.[72-74]

Inthesepatients,electivecesareansectionisusuallyrecommended under epidural orlow-dose combinedspinal-epiduralanesthesiaat34–36weeks.[73,74]Thetargetshouldbe to maintain sufficient pain control while minimizing adverseeffects.Earlyneuraxialanalgesia(epidural,combinedspinal–epidural) is recommended to reduce catecholamine-relatedcardiovascular stress due to labor pain. Controlled infusionanalgesiaorprogrammedintermittentbolustechniqueispreferred.Thegoalinnormallaborispainlessdeliverywithout significant motor block.[74] Appropriate volume replacementand,ifnecessary,avasopressorinfusioncanbeusedtominimizethevasodilatoreffectsofspinaland/orepiduralanesthesia.Mostanesthesiologistschooseacombinedspinal-epiduralapproach.Accordingtotheliterature,thematernalmortalityratehasbeenreportedtobesimilarinRAandGA(~20%).[73]

Comprehensiveknowledgeofpathophysiologicalchangesinpregnancyandmultidisciplinaryapproachwithrelated

specialties are needed for better anesthetic management ofpregnant with PH. Pregnant women have a higher risk ofdifficulty with airway and aspiration. Due to these risks andthevariablecardiopulmonarybalanceinpatientswithPH,RA should be preferred to GA whenever possible. It is suggestedthat these patients are followed-up in ICU.

Both pregnancy and PH predispose to thrombosis.[72-74] Themost common cause of mortality is RVF and PTE in theperipartumperiod.PregnantwomenwithPHundergoingRA haveahighriskofhematoma,andcareshouldbetakenintheperipa rtum period.[73,74] We prefer epidural anesthesia to reducesympatheticchargeandcontrolpainifsurgeryisnotemerge nt.

PostoperativeCareinPulmonaryHypertension

ThemostriskyperiodforPHpatientsundergoingnoncardiacsurg eryisthepostoperativeperiod.Thesepatientsarefollowedup in postanesthesia care unit (PACU) and ICU for the first48–72 h. Many patients with mild PH (mPAP <35 mmHg)undergoing low-risk and minor surgery can be effectivelymanaged in the PACU. Appropriate management of thesepatients with a multidisciplinary approach perioperativelywill reduce mortality and morbidity.[75,76] PACU staff shouldbegivenclearinstructionsregardingearlyphysiologicals ymptomsofdeteriorationsandbethoroughlyinformedabout who should be informed.[76,77] In our clinic, we followthepatientswithmildPHinPACUforthefirst24handthose withmoderateandseverePHinICUforthefirst48–72h.

PatientswithPHareathighriskofsuddenincreasesinPVR,arrhyt hmias, fluid shifts, PTE, ischemia, respiratory failure,andRVF.Themostcommoncausesofmortalityarerespirat oryfailure(60%)andRVF(50%).[3,23,47,48,76,77]

Asinacuterespiratorydistresssyndrome,aprotectiveventilator strategy should be used for patients on mechanicalventilation.[48]Hypercarbiaandacuterespiratoryaci dosismay develop with a protective ventilation strategy, whichmayincreasePVR.Therefore,theventilatorparametersm ust be adjusted accordingly. Hypoventilation and alveolarderecruitmentmayoccurduringspontaneousbreathingt rials.[10,37,48] Early mobilization and respiratory therapies areimportant to prevent atelectasis.[48] To prevent hypoxemia,oxygensupplementationmustbeprovided,andSpO $_2$mustbe$_{\text{kept above92\%.}}$[48,75,77,78]

Post-operative atelectasis may increase RV afterload, impairtheV/Qratio,andincreaseintrapulmonaryshunt.Inadditi on,atelectasismaycausefeverandthusincreasedmetabolicrate, oxygenconsumption,andeventuallyhypoxemia.Aggressivepu lmonarytoiletingisimportantforallPHpatientsandshouldbestart edasearlyaspossible.Spirometry,respiratorytherapy,and if necessary, noninvasive PPV with low PEEP should beperformedearly.[48,77,78]

Ensuring diuresis is critical in the postoperative period toprevent RV volume overload. Cardiac biomarkers such asPro-BNPandtroponinmaybeincreasedduetoRVoverload.

Thesemarkers,togetherwithperfusionmarkerssuchaslactate,$ScvO_2$andSvO_2maycontributetotheadjustmentofdiuretictherapy.[76] In patients with oliguric renal failure who do notrespondtodiuretictherapy,nephrologyconsultationisneededforcontinuousrenalreplacementtherapy,andadecisionshouldbemadebycommon consensus.[48,76-79]

Price*etal*.reviewed13clinicalstudieswithadultPH,8withPH undergoing endoscopy, 16 reviews, and 5case reportsfor patients undergoing GA or sedation for noncardiac andnonobstetric surgery. In these studies, 30-day mortality was2%–18%and15%–50%forelectivesurgeriesandemergencysurgery,respectively. ThemostcriticalcomplicationwasRVF.Moreover, they suggest that personalized preoperative riskevaluation,treatmentoptimization,andadvancedperioperativeplanningmay improve outcomes.[80]

Finally,themostcommoncausesofearlymortalityinpatients withPHarerespiratoryfailure,arrhythmia,andRVF.[26]Theincidenceofsurgeryforanyreasoninpatientswithpreviouslytreated orundiagnosedordiagnosedandincompletelytreatedPHcontinuestoincreaseworldwide.Anesthesiologistsneedtorecognizethesymptomsandsignscorrectlyinthepreoperativeevaluation to determine the safest anesthesia method and tomanagethepatientcorrectlyintheperi-operativeperiod,asitwillreducetheriskofcomplicationsanddeath.[2,3,10,20,23,26,37,48]Inourclinic,wehavecreatedamultidisciplinaryteam-basedapproachto(in)evaluatingpatientswithanesthesia.Inour study, which is in progress in our clinic, we evaluate thepostoperativefollow-up,importantriskfactors,andfirst30-day complications in the postoperative period, mortalityandmorbidity ofpreviously diagnosedpatients withPH.

Conclusion

Management of patients with PH peri-operatively requiresknowledge and experience. It is necessary to discuss thepatient'sshortandlong-termcaregoals,potentialdifficulties,and complications with a multidisciplinary team. The maingoalsinanesthesiamanagementareunderstandingthemainpathophysiology,optimizingfunctionalstatusandhemodynamics, managing comorbidities, and avoiding PHcrisis and RVF. A balanced anesthesia technique, includinginhalation agents, appropriate RA, and opioids may providethese patients steady hemodynamic profile. In PH patients,advancedintraoperativeandpostoperativefollow-up,pulmonaryvasodilatortreatments,adequateanesthesia,andanalgesiashouldbeconsidered.Itisessentialtooptimizethepatientforsurgeryin a nonemergency situation and to organize treatment andeducationofthepatientforthelong-termperiodofthedisease.

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Ethicalstatement

Theethicalstatementisnotapplicableforthisarticle.

Dataavailabilitystatement

Datasharingisnotapplicabletothisarticleasnodatasetsweregeneratedoranalyzedduringthecurrentstudy.

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