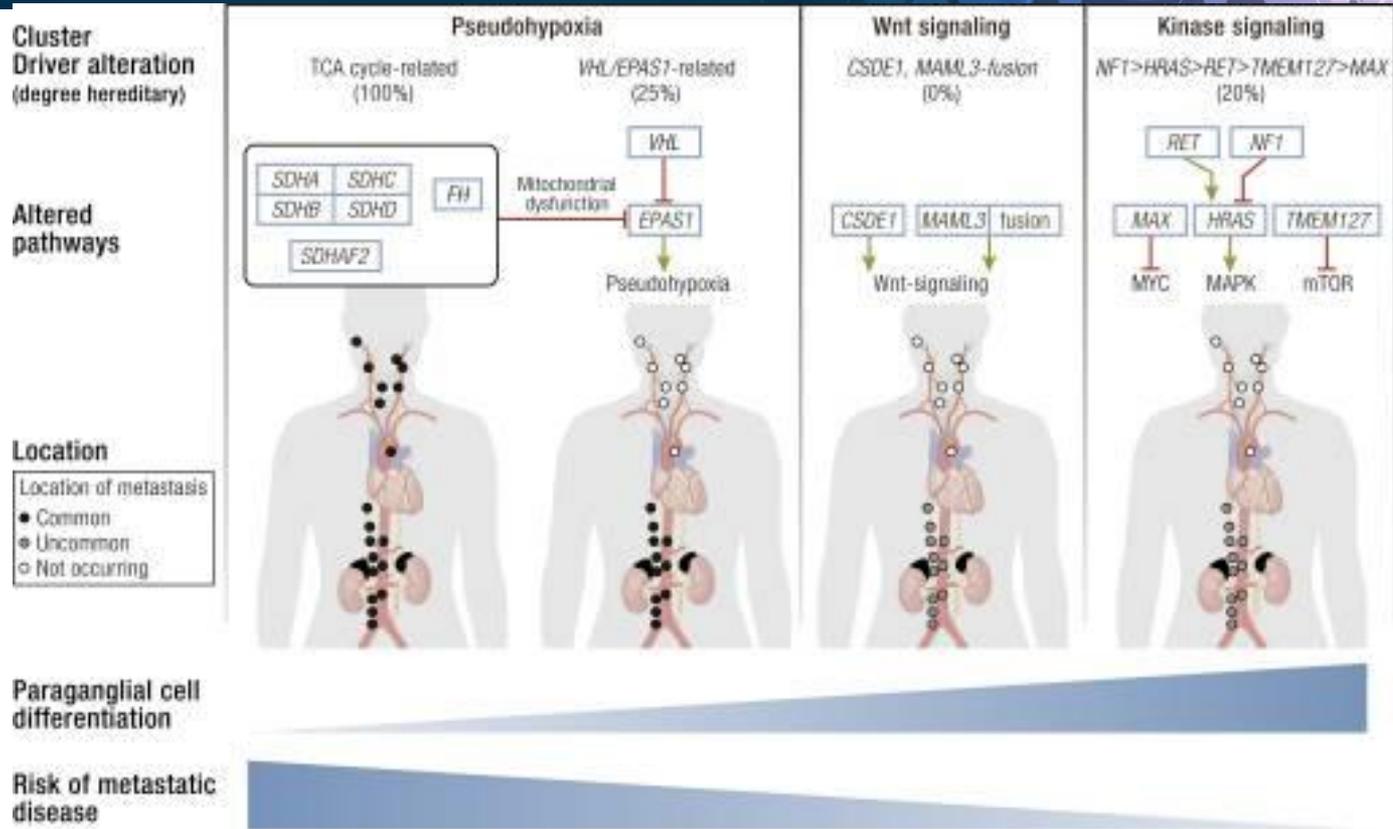


# ABORDAJE MULTIDISCIPLINAR DEL PARAGANGLIOMA METASTÁSICO

## Manejo de la hiperfunción hormonal

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H.U. 12 de Octubre

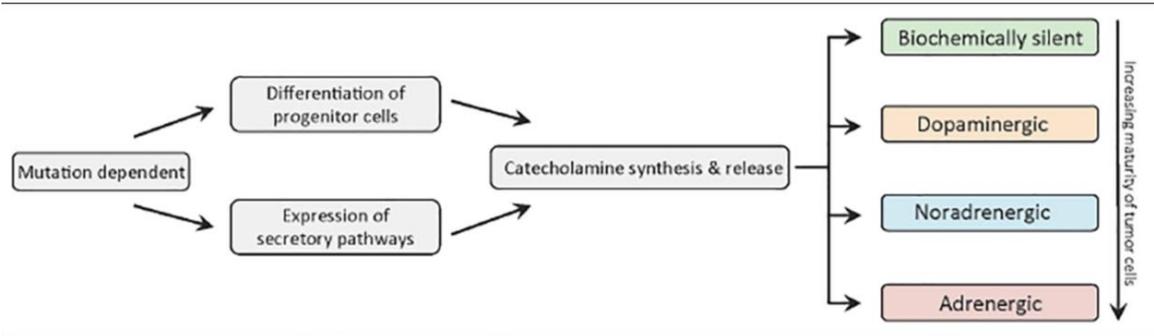


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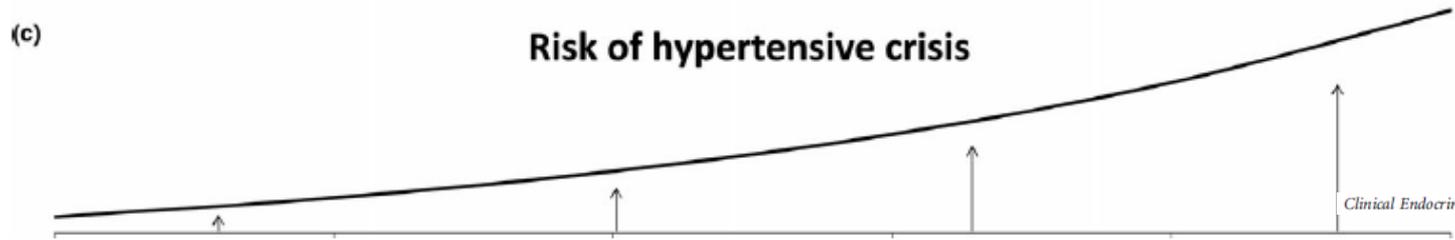
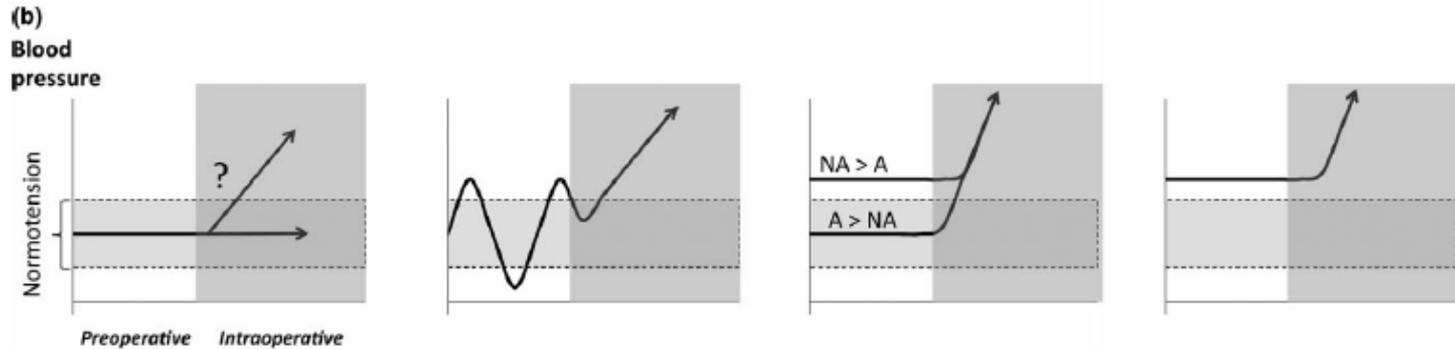
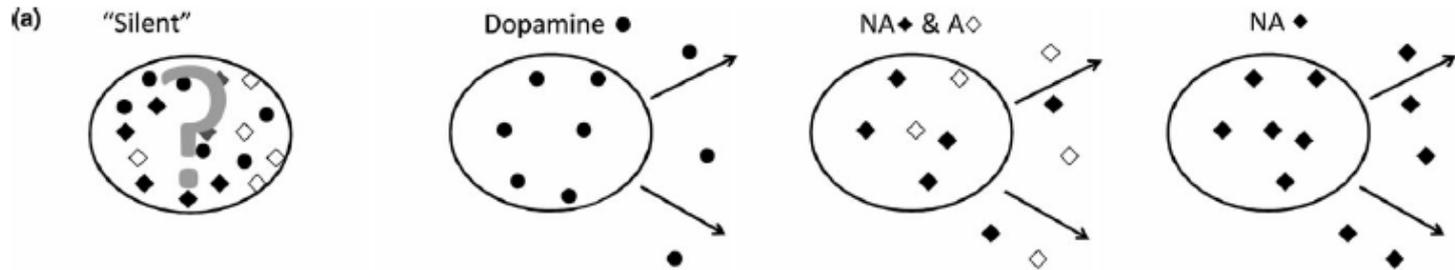
Fenotipo bioquímico



	DIANA	RESISTENCIA VASCULAR SISTÉMICA	FRECUENCIA CARDIACA	SISTEMA NERVIOSO SIMPÁTICO	ESTRÉS OXIDATIVO
ADRENALINA	Cél endoteliales Musculatura lisa vascular Receptores $\beta_2 > \beta_1$	↑↓	↑	↑	↑↓
NORADRENALINA	Musculatura lisa vascular Receptores $\beta_1 = \beta_2$	↑	↑	↑	↑
DOPAMINA	Vasculatura mesentérica y renal. Receptores D1	↓			



Biochemical phenotype	Primary receptor stimulated	Signs and symptoms	Clinical complications
Noradrenergic	$\alpha_1$ and $\beta_1$	Sustained HTN; Constipation; Sweating; Headache	Hypertensive crisis; Hypertensive encephalopathy; TIA and CVA; Intestinal ischemia; Optic neuropathy and retinopathy; Renal failure; Rhabdomyolysis
Adrenergic	$\beta_2$ , $\alpha_1$ and $\alpha_2$	Paroxysmal HTN; Palpitations; Anxiety; Diaphoresis; Flushing; Hyperglycemia; Hyperlipidemia	Severe hypotension; Hypertensive crisis; Cardiogenic shock
Dopaminergic	D1 and D2	Usually asymptomatic; Hypotension; Diarrhea; Nausea and vomiting	Dehydration
Biochemically silent	--	Asymptomatic	Possible hypertensive crisis during surgery



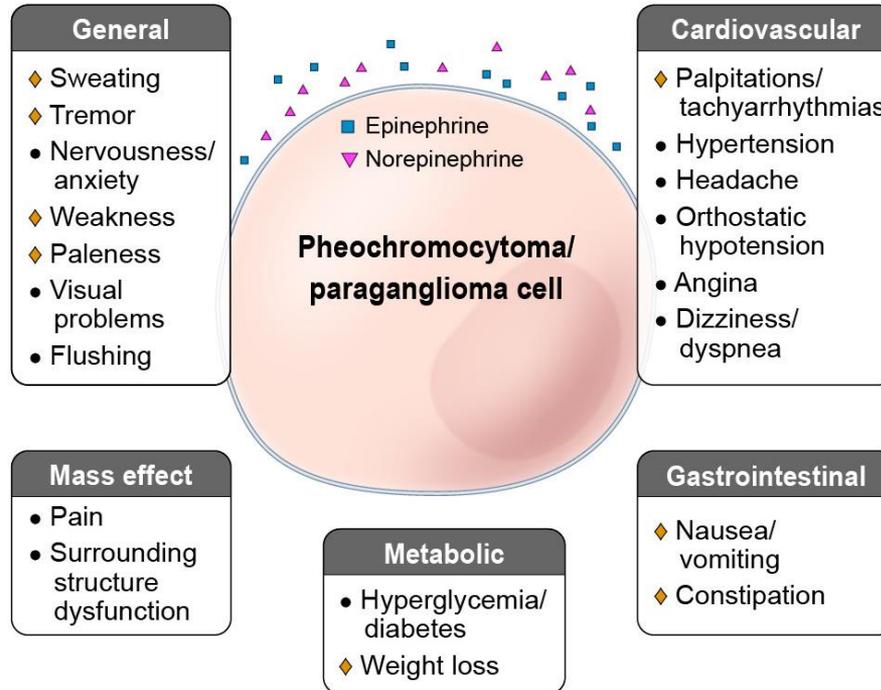
EN EL PPGL METASTÁSICO PODEMOS  
DISTINGUIR DOS SITUACIONES:

1. CONTROL DE LOS SÍNTOMAS

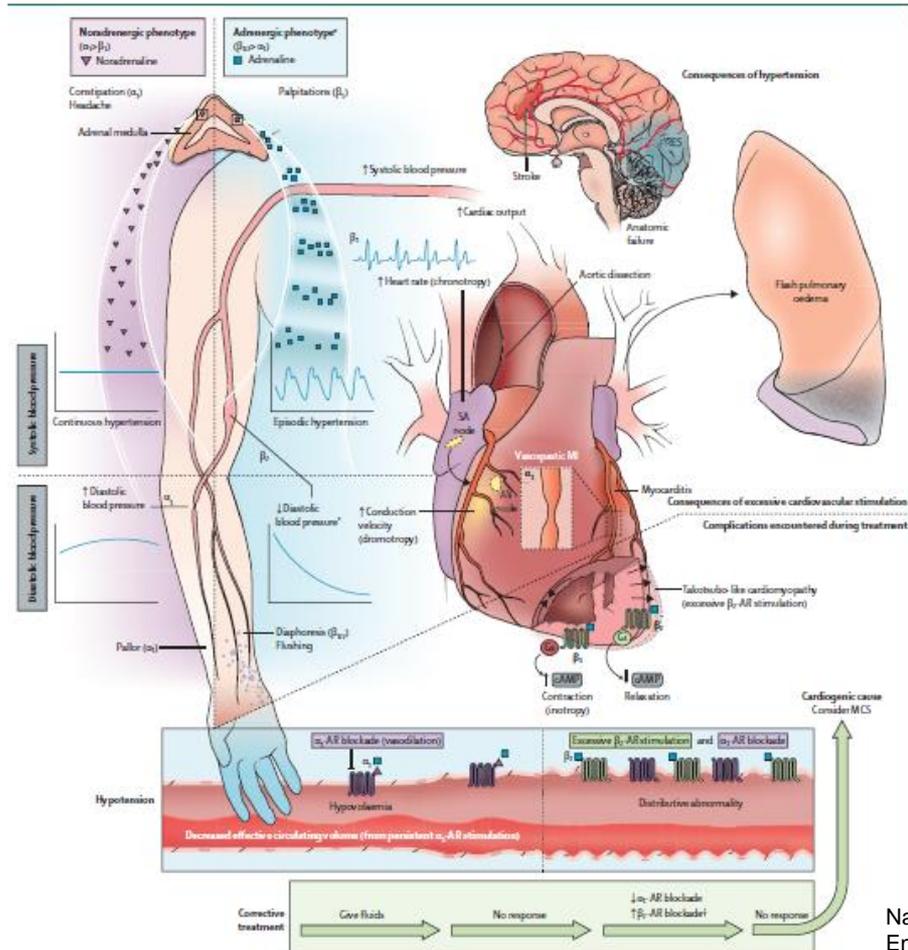
2. PREVENCIÓN CRISIS CATECOLAMINÉRGICA

# CLÍNICA

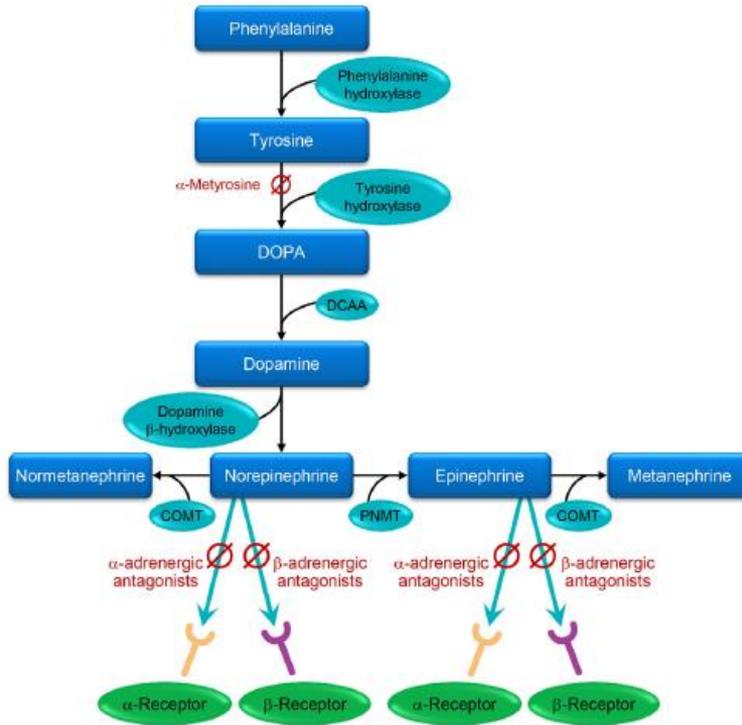
# SÍNDROME FUNCIONAL



# CRISIS CATECOLAMINÉRGICA



# MANEJO



DCAA = Aromatic Acid Decarboxylase  
 COMT = catechol-O-methyltransferase  
 PNMT = phenylethanolamine N-methyltransferase  
 DOPA = dihydroxyphenylalanine

Fig 1. Catecholamine synthesis pathway.

## OBJETIVOS:

Controlar los síntomas

Evitar complicaciones

Prevenir crisis

catecolaminérgicas

Poder implementar los diferentes  
tratamientos con seguridad

## INDIVIDUALIZACIÓN:

Fenotipo bioquímico

Comorbilidades y riesgo de

complicaciones

Situaciones de riesgo de crisis

Control dolor

Control toxicidad

Educación paciente

Alfa-bloqueo

Control HTA

Asociación otros hipotensores

Potenciar control HTA

Moderar efectos secundarios alfa-bloqueo

Beta-bloqueo

Control taquicardia

Prevenir arritmias y miocardiopatía

Manejo nutricional

Control hiperglucemia

Control síntomas gastrointestinales

Valoración ecocardiográfica basal

Contar con cardiología

# CONTROL DE LOS SÍNTOMAS CARDIOVASCULARES

	$\alpha$ -bloqueo	$\beta$ -bloqueo	Reposición volumen
Tratamiento	Doxazosina/fenoxibenzamida	Propranolol seguido de atenolol/metoprolol	Dieta rica en sal Ingesta de 2-3litros aguda/día Sueroterapia IV
Objetivos	TA <130/80mmHg sentado TAS >90mmHg de pie.	FC: 60-80lpm	Evitar ortostatismo
MANEJO PRE-INTERVENCIÓN			
Inicio	7-14 días antes de la cirugía	2-3 días antes de la cirugía	2-3 días tras inicio $\alpha$ -bloqueo

**TABLE 2 |** Brief instructions of preoperative drugs for pheochromocytoma and paraganglioma (PPGL).

Drugs	Doses	Starting time	Advantages	Adverse effects and points for attention	
α-AR antagonists	Phenoxybenzamine	Initially 10mg BID, usually 1mg/kg/d	1–2 weeks before surgery	The effect is profound and long-acting.	Prolonged hypotension postoperatively, orthostatic hypotension, reflex tachycardia, nasal congestion, central sedation Orthostatic hypotension, the anti-hypertensive effect may not as profound as phenoxybenzamine
	Prazosin	Initially 0.5–1 mg BID-TID, usually 6–15 mg/d, maximum dose of 20 mg/d		Lower risk of postoperative hypotension, seldom cause reflex tachycardia, nasal congestion and central sedation	
	Perazosin	Usually 2–10 mg/d, maximum dose of 20 mg/d			
	Doxazosin	Initially 1mg QD, usually 2–8 mg/d, maximum dose of 16 mg/d			
β-AR antagonists	Propranolol	Initially 10 mg TID-QID, maximum dose of 200 mg/d	After adequate α-AR blockade	Long-acting	Never be used alone or before adequate α-AR blockade, should not be used for patients with asthma, severe atrioventricular block or bradycardia, sick sinus syndrome, severe heart failure, and cardiogenic shock
	Atenolol	Usually 12.2–25 mg BID-TID			
	Metoprolol	Usually 25–50 mg BID-TID			
	Metoprolol controlled release tables	25–200 mg QD			
CCBs	Nicardipine	Initially 20 mg TID, maximum dose of 120 mg/d	1–2 weeks before surgery if necessary	Do not cause drug-induced orthostatic hypotension and reflex tachycardia, prevention of CA-mediated coronary vasospasm and myocarditis	Monotherapy of CCBs may not be effective enough for patients with biochemically active PPGL, which should be combined with α-AR antagonists.
	Amlodipine	5–10 mg QD			
	Nifedipine	Initially 10mg TID, maximum dose of 120mg/d			
	Nifedipine controlled release tables	30-60mg QD			
CA synthesis inhibitor	Metyrosine	Initially 500 mg/d, maximum dose of 4 g/d	At least 1–3 weeks before surgery	Directly inhibit the CA biosynthesis	Sedation, somnolence, anxiety, depression, and rarely leading to extrapyramidal signs (such as parkinsonism)

## CONTROL DE LOS SÍNTOMAS

	Fenoxibenzamida	Bloqueantes alfa1- selectivos
Disponibilidad	Medicamentos extranjeros	<b>Oficinas de farmacia</b>
Acción	Antagonista $\alpha_1$ y $\alpha_2$	<b>Antagonista <math>\alpha_1</math></b>
Vida media	24hs	<b>16-36hs</b>
Efectos secundarios	Ortostatismo ++++ Taquicardia refleja++++ Astenia marcada++++ Congestión nasal Inhibición eyaculación	<b>Ortostatismo ++</b> <b>Taquicardia refleja ++</b> <b>Astenia ++</b>

**Table 3.** Catecholamine-related outcomes following metyrosine use in pheochromocytoma and paraganglioma

Author, year, and study design	Patient characteristics	Tumor characteristics	Metyrosine	Outcome
Engleman, 1968 (8)	N = 22	Pheochromocytoma	Daily dose: 600-4000 mg	<ul style="list-style-type: none"> <li>• Urinary catecholamines reduced by 20%-79%</li> <li>• 68% of patients had at least a 50% reduction in urine catecholamines</li> <li>• 82% of patients had clinical or symptomatic improvement</li> </ul>
Prospective	Mean age 39.1 y (range, 13-73)	Metastatic disease (32%)	Duration: mean 12 days	
Single center	Female 36%			
Naruse, 2018 (9)	N = 16	Pheochromocytoma and paraganglioma	Chronic therapy (n = 13):	<p>Overall:</p> <ul style="list-style-type: none"> <li>• 31.3% of patients with at least 50% reduction in urine Metanephrines, urine normetanephrines</li> </ul> <p>Patients on chronic therapy:</p> <ul style="list-style-type: none"> <li>• 62% reported mild improvement in catecholamine symptoms; 38% with no change in symptoms</li> </ul> <p>Patients treated preoperatively only:</p> <ul style="list-style-type: none"> <li>• 23.1% had at least 50% reduction in urine catecholamines</li> <li>• 66.7% had at least 50% reduction in urine catecholamines</li> </ul>
Prospective	13, chronic therapy 3, preoperative therapy		Daily dose: mean 1028 ± 507 mg	
Multicenter	Mean age 54.8 y (range, 12-86)		Duration: mean 124.9 ± 64 d	
Open label	Female 45%		Preoperative therapy (n = 3):	
			Daily dose: mean 1083 ± 629 mg	
			Duration: mean 53.5 ± 27.2 d	

## PREVENCIÓN CRISIS

- **SITUACIONES DE RIESGO:**
  - **Cirugía**
  - **Biopsia**
  - **Terapia locorregional ( Radiofrecuencia, Quimioembolización,...)**
  - **Administración PRRT**

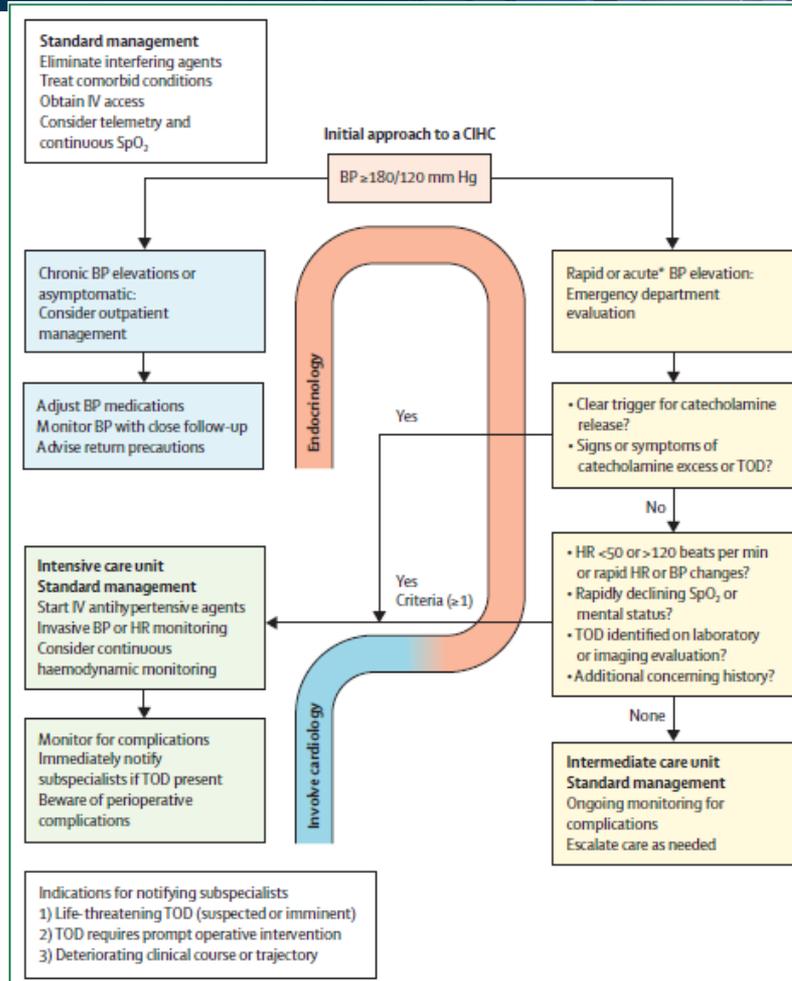
## PREVENCIÓN CRISIS

**IDENTIFICAR PACIENTES  
MAYOR RIESGO**

**PREVIO AL PROCEDIMIENTO**

**TRAS PROCEDIMIENTO**

# CRISIS CATECOLAMINÉRGICA



## CONSIDERACIONES IMPORTANTES EN EL CONTROL DE LOS SÍNTOMAS

- **Requiere adaptar objetivos de control , fármacos y dosis**
- **Teniendo en cuenta:**
  - **Grado de secreción hormonal**
  - **Complicaciones**
  - **Estado basal del paciente**
  - **Pronóstico**
  - **Respuesta a tratamiento sistémico instaurado**

## CONSIDERACIONES IMPORTANTES EN PREVENCIÓN CRISIS

- **En situaciones de riesgo:**
  - **Asegurar adecuado alfa y beta-bloqueo previo**
  - **Asegurar una adecuada monitorización durante y tras el procedimiento.**
  - **Adecuar el tratamiento tras el procedimiento para prevenir complicaciones (hipotensión, hipoglucemia).**

