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Organ specialists coping with geriatric patients

Heart Failure (Part 2)☆

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ABSTRACT

The treatment for heart failure (HF) caused by systolic dysfunction (heart failure with reduced ejection fraction, HFREF) is currently better defined than that of HF caused by diastolic dysfunction (heart failure with preserved ejection fraction, HFPEF). Available drugs include blockers of the renin-angiotensin-aldosterone system (i.e. angiotensin-converting enzyme inhibitors, angiotensin II AT-1 receptor blockers, aldosterone antagonists, direct renin inhibitors), beta blockers, diuretics, nitrate derivatives and digoxin. When HF stage III-IV with left ventricular ejection fraction less than 35% and QRS complexes greater 120 ms persist despite optimal medical therapy, cardiac resynchronization therapy (CRT) yields a benefit in the majority of cases, both in terms of quality of life and reduction in mortality.

1. Treatment

The treatment for heart failure (HF) caused by systolic dysfunction (HFREF) is currently better defined than that of HF caused by diastolic dysfunction (HFPEF) [1].

1.1. Available medication

Certain drugs (renin-angiotensin-aldosterone system (RAAS) inhibitors, beta-blockers) improve symptoms and slow progression of ventricular dysfunction, thereby reducing morbidity and mortality [2].

Others, such as loop diuretics, thiazides or nitrate derivatives treat symptoms but have no effect on the evolution of the disease.

Digoxin plays a special role thanks to its double cardiotonic and anti-arrhythmic action.

1.1.1. Renin-angiotensin-aldosterone system (RAAS) inhibitors

There are four RAAS inhibitors, namely : angiotensin-converting enzyme inhibitors (ACEI), angiotensin II AT1-receptor blockers (ARBs), aldosterone antagonists and direct renin inhibitors (DRI).

1.1.1.1. Angiotensin-converting enzyme inhibitors (ACEI). By blocking the transformation of angiotensin I into angiotensin II, ACEI prevent vasoconstriction caused by angiotensin II, as well as the fluid retention and fibrosis provoked by aldosterone. The beneficial effect on morbidity and mortality when ejection fraction (EF) is less than 40% is widely acknowledged [3–5].

Although all the molecules in this pharmaceutical class have not been tested in the same trials, there is likely a class effect that is specific to all ACEI.

However, ACEI do not prevent the appearance in the long term of a variable plasma concentration of aldosterone, which can be sufficient to cause related adverse effects (e.g. fluid retention, fibrosis).

Several factors can explain this "escape phenomenon". First, the usual doses of ACEI, which often cannot be increased because of hypotension or renal insufficiency, are not sufficient to suppress adrenal production of aldosterone commanded by angiotensin. Second, excessive salt restriction (< 3 g/day) and loss of sodium due to loop diuretics provoke secretion of aldosterone linked to the angiotensin-independent regulation of intravascular volume. Third, it is hypothesized that cardiomyocytes in the dysfunctional ventricle produce elevated levels of aldosterone [6–8].

Aldosterone receptor antagonists can counteract this escape phenomenon. It has been shown that adding 25 mg of spironolactone, and more recently, eplerenone to ACEI treatment significantly reduced mortality and hospitalisation for heart failure, without inducing hyperkalaemia, although patients with kalaemia greater than 5 mmol/L and creatinaemia greater than 220 μmol/L were not included [9,10].

A moderate and transitional elevation of urea and creatinine is often observed early after initiation of ACEI treatment, but this is not a contra-indication. However, ACEI are contra-indicated in the presence of severe renal failure.

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The main side effect of ACEI is a chronic dry cough and persistent sore throat (15–20% of cases, regardless of the molecule under consideration), due to a reduction in catabolism of bradykinin, which stimulates pulmonary C fibres, hence the cough.

In this case, ACEI should be replaced by ARBs, bearing in mind that both are contra-indicated in case of severe aortic stenosis.

1.1.1.2. Angiotensin II AT1-receptor blockers (ARBs). ARBs inhibit the RAAS one stage later than ACEI, by blocking angiotensin II AT_1-receptors, thus allowing free production of angiotensin II. After ACEI, which they can replace when ACEI are poorly tolerated, ARBs are considered to be as efficacious in case of EF less than 40% [1,11].

There are several ARBs currently available, and there likely exists a class effect, as for ACEI. Among ARBs, only losartan is uricosuric [12].

ARBs link only very weakly with other receptors, such as AT_2, whose stimulation by angiotensin II seems to exert potentially beneficially vasodilator and anti-proliferative effects. The addition of an ARB to ACEI therapy can thus be useful in certain forms of refractory HF [13].

Current recommendations advocate the use of ARBs in case of ACEI intolerance [1]. Since ARBs do not inhibit the catabolism of bradykinin, the risk of irritating chronic cough is lower, although it exists nonetheless, for reasons that remain to be elucidated.

1.1.1.3. Aldosterone antagonists. Aldosterone antagonists (spironolactone, eplerenone, soluble potassium canrenoate) share the fourfold properties of blocking the last stage of the RAAS, favouring elimination of sodium in urine, counteracting depletion of potassium and magnesium induced by other diuretics and tempering tissue fibrosis[1] [14].

They are useful in association with ACEI or loop diuretics.

Aldosterone blockade has even been reported to significantly reduce mortality [14].

However, therapy with spironolactone should be interrupted if kalaemia exceeds 5 mmol/L or if glomerular filtration rate is less than 30 mL/min.

In elderly patients, who often have impaired renal function, a daily dose of 12.5 mg of spironolactone (instead of 25 mg) reduces the risk of hyperkalaemia.

The progestative and antiandrogenic effects of spironolactone can give rise to mastodynia or gynecomastia. In this case, eplerenone, a newer and more selective aldosterone antagonist, should be preferred at the same doses [15].

1.1.1.4. Direct renin inhibitors (DRI). The more recent DRIs block the first stage of the RAAS by preventing the transformation of angiotensinogen into angiotensin I by renin.

The first DRI, namely aliskiren, became commercially available in 2007 and is recognised in the treatment of hypertension. It is soon likely to be approved for the treatment of HF, perhaps associated with an ACEI or an ARB, as their mechanism of blocking the RAAS increases the secretion of renin.

It can thus be seen that several pharmaceutical combinations of RAAS blockade are possible, and the future will reveal which are the most effective [16]. However, in all instances, the potential benefit should be assessed in perspective with the total number of drugs needed to treat the whole disease.

1.1.2. Beta-blockers

HF is invariably accompanied by the activation of the sympathetic nervous system and the level of noradrenaline increases in accordance with the severity of the disease. Catecholamines stimulate beta-1 and beta-2 receptors, which are present in the heart at a rate of 80% and 20% respectively. This increased stimulation in HF leads to a reduction in the sensitivity and quantity of beta-1 receptors, so-called "down regulation", almost like denervation of the heart.

Furthermore, noradrenaline increases the concentration of cyclic AMP, thus also increasing concentrations of intracellular calcium, leading to oxidative stress and eventually, programmed cell death (apoptosis) [17].

In the context of HF, beta-blockers exert two opposite effects, as a function of time.

First, early after treatment initiation, they actually worsen cardiac function through cardiac depression and negative hemodynamic effect.

However, after about one month of treatment, beta-blockers reduce symptoms of HF and improve tolerance to effort and cardiac function, through a positive neuro-hormonal effect.

Thus, they improve survival in patients with EF less than 40% [18–21].

Beta-blockers should initially be prescribed at low doses, and increased gradually, generally accompanied by a RAAS inhibitor and a diuretic.

Only bisoprolol, metoprolol, carvedilol and nebivolol have been studied in clinical trials; however, this does not rule out the existence of a class effect.

Recap of the main properties of certain beta-blockers:

- bisoprolol, metoprolol, nebivolol and atenolol are cardioselective, as they inhibit only beta-1 receptors [22]. They should be preferred in patients with broncho-pulmonary disease, bearing in mind that the cardioselectivity tends to decrease with increasing dose, and secondly, chronic obstructive pulmonary disease (COPD) is not a contra-indication for use of beta-blockers, contrary to true asthma;
- metoprolol is highly liposoluble, whereas bisoprolol and carvedilol are only moderately liposoluble. The liposolubility ensures better gastric absorption, and also allows better uptake of the drug in the central nervous system, albeit with more side effects (fatigue, headache, insomnia, depression) [22];
- atenolol and sotalol are water soluble, with the opposite advantages and disadvantages to the liposoluble molecules. Paradoxically, sotalol has an anti-arrhythmic effect (class III, amiodarone-like), independently of its adrenolytic properties, and a potential arrhythmogenic effet linked to a possible prolongation of the QT interval;
- carvedilol and nebivolol cause peripheral vasodilation, which can be a useful property in case of arteriopathy [22].

In diabetic patients under insulin beta-blockers can mask symptoms of hypoglycaemia, such as tremor and tachycardia, but not sweating [22].

Beta-blockers that are not beta-1 selective, i.e. those that also inhibit beta-2 receptors, can cause a rise in triglycerides of approximately 25%, and lower HDL cholesterol by about 15%. Cardioselective beta-blockers can interfere with the lipid profile to a lesser degree. The clinical significance of these biological modifications has never been shown, because, by curious paradox, beta-blockers with sympathicomimetic effects (pindolol, bopindolol) have more or less no effect on lipid profile, but are less efficacious than other beta-blockers in the reduction of mortality after myocardial infarction [23,24].

1.1.3. Diuretics

Long established and relatively inexpensive, diuretics relieve the patient by reducing fluid retention.

[1] Aldosterone antagonists counteract the mineralocorticoid effects of aldosterone, but unlike ACEI and ARBs, do not affect vasoconstriction induced by angiotensin II.