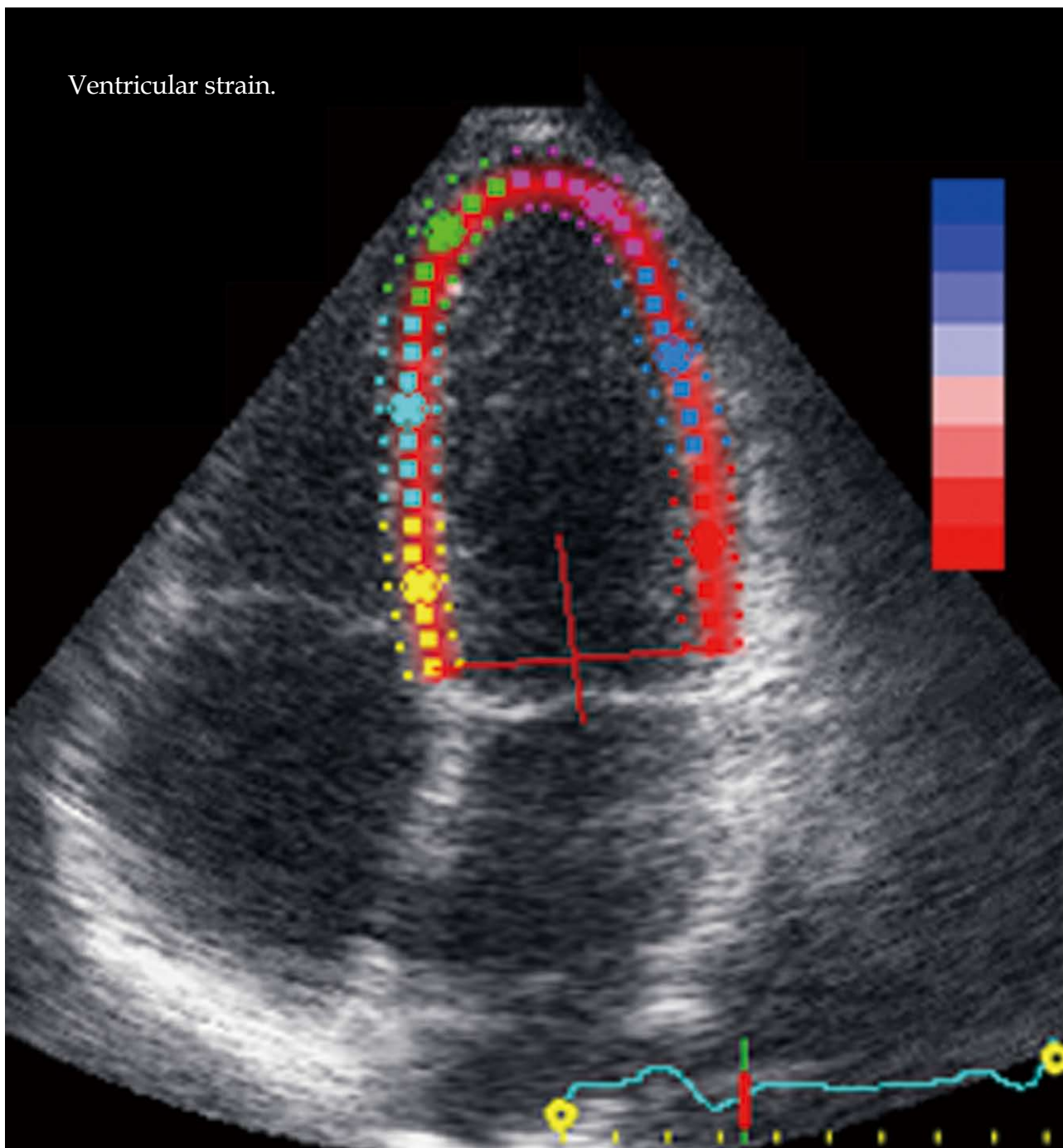
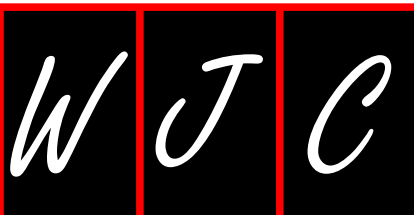




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Heart regeneration: Past, present and future

Adriana Bastos Carvalho, Antonio Carlos Campos de Carvalho

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INTRODUCTION

For most of the last century, the heart has classically been viewed as an organ incapable of self-renewal^[1]. The basis for this assumption was laid more than eight decades ago and many still consider it a definitive characteristic^[2,3]. However, the possibility of cardiac self-renewal has been re-examined over the years^[4-6]. Here, we will review heart regeneration research from a historical perspective, presenting the foundations that established the field. Then, we will discuss current knowledge and future possibilities for this exciting and promising area of research.

PAST

From 1850 to the first quarter of the 20th century, the prevailing view among cardiologists was that the heart was capable of regeneration, since organ hypertrophy was attributed to cardiomyocyte hyperplasia^[2,4]. In 1925, Karsner *et al*^[2] examined in detail whether macroscopic cardiac hypertrophy was caused by an increase in the size or in the number of fibers present in adult cardiac muscle. By counting the nuclei stained with hematoxylin and eosin, they concluded that the number of cardiac fibers was unchanged in the hypertrophied human heart when compared to a normal heart, indicating that hypertrophy was caused by enlargement rather than proliferation of cardiomyocytes. Additionally, they also stated that "the most careful search has failed to disclose mitotic figures". These observations laid the ground for envisaging

Abstract

The heart has been considered a post-mitotic organ without regenerative capacity for most of the last century. We review the evidence that led to this hypothesis in the early 1900s and how it was progressively modified, culminating with the report that we renew 50% of our cardiomyocytes during our lifetime. The future of cardiac regenerative therapies is discussed, presenting the difficulties to overcome before repair of the diseased heart can come into clinical practice.

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Key words: Cardiomyocyte proliferation; Cardiac stem cells; Self-renewal; Stem cell-based therapies

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the heart as a post-mitotic organ, which is a view that became common knowledge and remained widely accepted for much of the last century.

In spite of this, already in 1937, Macmahon^[4] demonstrated that, even though mitotic figures had not been found in the adult heart, they were present in the hearts of children with hypertrophy and myocarditis. Additionally, Robledo^[7] published work in 1956 demonstrating the presence of mitosis in 4 to 7 d old rats that had been submitted to myocardial injury by burning a small ventricular area.

The first evidence that not only young but also adult hearts could regenerate was presented in 1960. Linzbach^[5] published an article analyzing the anatomic basis of variations in the size of the human heart. First, the average length of sarcomeres, as measured by the distance between Z-bands, was shown to be unchanged in normal, hypertrophied and dilated hearts. Then, it was demonstrated that, when the adult heart was pathologically overloaded and its weight exceeded 500 g (or 200 g for the left ventricle), there was an increase in the number of muscle fibers with little further thickening of these fibers. Hence, even though cardiomyocyte proliferation had not been directly documented, the addition of new fibers suggested that some form of cardiac regeneration had occurred in the adult heart.

In the following years, mitosis started to be documented in uninjured cardiac muscle^[8,9]. In 1968, Sasaki and co-workers described that mitotic figures could be found in normal rats treated with colchicine, both in cardiomyocytes (at the age of 4 wk) and interstitial cells (at 6 mo)^[8]. Moreover, Zak^[9] published a famous review in 1974 discussing the proliferative capacity of cardiac muscle cells. He described, as shown by Sasaki, that cardiomyocytes can undergo mitosis in rats up to 4 wk of age. In addition, he also analyzed the presence of mitosis in other organs; e.g. in the liver no mitotic figures could be found 10 wk after birth, which is, as concluded by the author, an indication that proliferation will stop in any organ that has achieved its adult size. The aspect that really differentiates the liver from the heart is the proliferative capacity in response to injury in adult cells. Zak stated that adult cardiomyocytes were unable to divide in a pressure overload model, although there was proliferation of non-muscle cells, which is a fact that had not been appreciated previously. Therefore, he concluded that cardiac hypertrophy consists of hypertrophy of myocytes and hyperplasia of connective tissue cells, thus reinforcing the notion of the cardiomyocytes as post-mitotic cells.

In 1977, Astorri *et al.*^[10] published an article confirming Linzbach's findings in diseased adult human hearts, demonstrating that cardiomyocyte hyperplasia was evident above the critical left ventricular weight of 250 g. Nonetheless, no direct evidence of mitosis in adult cardiomyocytes had yet been found. Only in the 1990s did the evidence start to appear^[6,11-13]. Quaini *et al.*^[6] demonstrated the presence of proliferating cell nuclear anti-

gen, expressed at the G₁-S boundary of the cell cycle, in adult cardiomyocytes obtained from ischemic and dilated cardiomyopathy patients. However, DNA synthesis and nuclear division do not provide definitive evidence of mitosis in cardiomyocytes since these cells can undergo DNA duplication and karyokinesis, becoming multinucleated without dividing (no cytokinesis). A few years later, the presence of both metaphasic chromosomes and cytokinesis was detected in normal myocardium^[12,13] in ischemic and dilated cardiomyopathy patients^[12], as well as in patients who had suffered a myocardial infarction^[13].

From that point on, it became generally accepted that cardiomyocytes could proliferate in the adult heart. However, there was no agreement on the frequency of this event in normal and diseased myocardium. As reviewed by Soonpaa *et al.*^[14], the frequency of cell division is influenced by the methods used to detect DNA synthesis and identify cardiomyocytes. In normal adult rats and mice, the percentage of cardiomyocytes that were synthesizing DNA is reported to range from 0.005%-3.15% and 0.0004%-0.04%, respectively^[14]. In the injured hearts of adult animals, results were even more variable, ranging from 0.0006%-43.6% in rats and 0.0055%-0.5% in mice^[14].

Thus, even though cardiomyocyte proliferation was accepted by the scientific community, the discrepancies found in the frequency of mitosis led to universal disagreement on the biological significance of this event. Based on clinical observations, several authors argued that cardiomyocyte proliferation had no biological significance since the heart was unable to recover, for instance, from myocardial infarctions and that primary heart tumors were rarely observed in adults^[14,15]. However, as pointed out by Anversa *et al.*^[16], regardless of the proliferative capacity of their parenchymal cells, the outcome of infarction is identical in several organs, including the testis, skin, kidney, brain and intestine. Additionally, using the rarity of primary heart tumors as an argument is also faulty; despite the fact that neurons do not usually proliferate, there are several tumors that arise from the interstitial/supporting cells in the central nervous system. On the other hand, although the heart also has a vast number of interstitial/supporting cells, tumors originating from these cells are as rare as the ones originating from cardiomyocytes. This could possibly indicate that the infrequency of primary heart tumors has more to do with the structural, mechanical and functional characteristics of the organ than with the rate of cardiomyocyte proliferation.

Therefore, no agreement on the importance of cardiac self-renewal was reached and new facts would come to play a role. In the late 1990s, we moved into the present stage with the explosion of stem cell research directed toward regenerative medicine.

CURRENT PERSPECTIVES

Stem cell research was actually implemented in the early

1960s after the observation that lethally irradiated mice could be rescued from death by a bone marrow transplant^[17,18]. Till and McCulloch began to analyze the bone marrow to find out which component was responsible for regenerating blood, leading to the discovery of the hematopoietic stem cell^[18-20]. However, it was only in the late 1990s that scientists started trying to use bone marrow stem cells (BMCs) to regenerate injured organs such as skeletal muscle^[21], brain^[22,23], liver^[24,25] and heart^[26,27]. From this moment on, stem cell research applied to regenerative medicine grew exponentially and a few years later, in 2004, the capacity of BMCs to regenerate the heart started to be challenged^[28-31]. In the mean time, a number of clinical trials using bone marrow-derived cells were started. The majority of these trials used the mononuclear fraction of the patient's own bone marrow. The results have been far more modest than was anticipated, with reported gains of 3%-4% in left ventricular ejection fraction in acute myocardial infarction patients.

From the point of view of cardiac self-renewal, it is not important whether BMCs can or cannot transdifferentiate into cardiomyocytes. In fact, the importance of those disputed initial findings resides on the fact that they triggered the search for resident stem cells in the heart. The first report of such a cell appeared in 2002, indicating the presence of a verapamil-sensitive side population (SP) with stem cell-like activity^[32]. Shortly after, the existence of several other types of cardiac stem cells was reported: c-kit positive^[33], Sca-1 positive^[34,35], cells with persistent expression of Abcg2^[36], cardiosphere-derived cells (CDCs)^[37] and islet-1 positive cells^[38,39]. Since only c-kit positive^[40], CDCs^[41] and islet-1 positive^[38,42] cells were isolated from human tissue, these cell types have received more attention over the years.

Human c-kit positive cells isolated from small samples of myocardium are self-renewing, clonogenic, multipotent and have the ability to generate cardiomyocytes and coronary vessels *in vivo*, improving cardiac function after myocardial infarction in mice^[40]. CDCs isolated from human endomyocardial biopsies form a heterogeneous population that expresses antigens found in other stem cell types, such as c-kit, CD90 and CD105^[41]. When co-cultured with rat neonatal cardiomyocytes, CDCs exhibited calcium transients synchronous with the neighboring myocytes and, when injected *in vivo*, engrafted and improved cardiac function in mice submitted to myocardial infarctions^[41]. Islet-1 is a developmental lineage marker for undifferentiated cardiogenic precursor cells usually found in the fetal human heart^[38]. After birth, few islet-1 positive cells can be found in the myocardium, suggesting they are developmental remnants of the fetal progenitor population. These cells can be isolated and differentiated into fully mature cardiomyocytes that express contractile proteins, generate calcium transients and respond to β -adrenergic stimulation^[38]. However, their presence in the adult human heart and their capacity to engraft, regenerate myocardium and improve cardiac function in animal models remains to be demonstrated.

As pointed out by Laflamme *et al.*^[43], it is unlikely that the heart would harbor multiple non-overlapping sets of cardiomyocyte progenitors. However, some degree of overlapping has been reported; a subset of c-kit positive cells do express Sca-1^[33], CDCs are formed by a heterogeneous population in which c-kit expression has been documented^[37,41] and islet-1 positive cells may not exist in adult myocardium at all. Furthermore, it is possible that these cell types are precursors originating from a more undifferentiated cell that would be the true cardiac stem cell. Regardless of which cell is the right one, the major advance pushed forward by the isolation of cardiac stem cells is the possibility that the heart possesses progenitors that are responsible for the physiological renewal of cardiomyocytes, which involves a slow turnover process, maintaining organ homeostasis. Obviously, these cells cannot fully recover the myocardium in pathological conditions, but even in this scenario some degree of regeneration has already been reported. Hsieh and co-workers, using α -myosin heavy chain *Cre-Lox* transgenic mice, elegantly demonstrated that up to 15% of cardiomyocytes could be regenerated in adult hearts after myocardial infarction^[44].

Finally, definitive evidence that the human heart is capable of self-renewal came in 2009. Bergmann and co-workers^[45] published an important study in which they used the integration of carbon-14, generated by nuclear bomb tests during the Cold War, into DNA to establish the age of cardiomyocytes composing the human heart. They reported that 1% of human cardiomyocytes are renewed annually at the age of 25 and that this rate is reduced to 0.45% at the age of 75. Moreover, total cell renewal over the entire human life span corresponds to approximately 50% of the cardiomyocytes.

Therefore, we can go back to reflect on the end of the 1990s when there was no agreement on the biological significance of cardiac self-renewal. It is now undeniable that heart regeneration does occur and is important to maintain organ homeostasis. This regeneration is probably a result of both stem cell differentiation and cardiomyocyte proliferation. It is now time to move forward and explore all the possibilities that these new advances have opened in the field.

FUTURE POSSIBILITIES

It is impossible to talk about the future of regenerative medicine and cardiac regeneration without mentioning the truly pluripotent cells. Embryonic stem cells (ESC) and induced pluripotent stem cells (iPSC) are unquestionably able to generate any cell type in our body and therefore have an insurmountable potential for regeneration. Obvious problems to be overcome are immune rejection (in the case of ESC) and the carcinogenic potential of both cell types. Pre-differentiation of patient specific iPSCs into the desired cell type for transplantation can potentially avoid both immune rejection and carcinogenesis, but differentiation protocols into a

specific cell type are still of very low efficiency. Derivation of iPSCs without true teratoma formation capacity, viewed as a problem for the field^[46], can in fact provide an important advantage for these cell lines in regenerative medicine.

Fast progress seen in the development of defined culture media, free of animal antigens, and stringent purification and expansion of pre-differentiated cells, anticipate the use of pluripotent derived cells in clinical trials in the future.

Use of the cardiac stem/progenitor cells also has great potential for future clinical use. In fact, clinical trials using CDCs and c-kit positive cells are currently underway in California and Louisville, KY, respectively. Advantages include the use of a multipotent cell type, thus unlikely to promote carcinogenesis, and use of autologous cells, since they are derived from biopsies obtained from the heart muscle of the patient. Potential disadvantages are the diminished numbers and regenerative potential of stem cells derived from a diseased organ. Heesch *et al.*^[47] have shown a decrease in colony forming and migration capacity of bone marrow cells obtained from patients with ischemic heart disease.

Introduction or re-introduction of exogenously cultured cells (either genetically or non-genetically manipulated) is the immediate future for cardiac regeneration strategies, but long term goals include use of factors that are capable of enhancing endogenous regeneration and genetic interventions using viral delivery systems. Knowledge gained from pre-clinical and clinical trials using the exogenous cells will allow insights into the relevant factors needed to boost the regenerative capacity of our own stem cells. Another approach would be the genetic manipulation of the cardiomyocyte cell cycle, inducing genes responsible for proliferation after the regulatory mechanisms involved in this event are elucidated^[48].

Finally, a word of caution is offered. Although we may discover the best cell type, administration route and time-window for the regeneration of the diseased heart, some questions remain open. The improvement in cardiac function, our ultimate goal, will depend on the long-term engraftment of the injected cells. In that regard, the results reported by Wu's group have been truly "disheartening"^[49,50]. Using bone marrow derived, cardiac derived or pluripotent derived cells in animal models of ischemic heart diseases, Wu and coworkers have been unable to detect cell survival for more than a few weeks in the heart. This may be the last and most difficult obstacle to conquer: a way to induce permanent engraftment of the injected cells.

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Heart failure in subjects with chronic kidney disease: Best management practices

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Abstract

Renal dysfunction is common in patients with heart failure (HF) and can complicate HF therapy. Treating patients with HF and kidney disease is difficult and requires careful assessment, monitoring and balancing of risk between potential benefits of treatment and adverse impact on renal function. In this review, we address the pathophysiological contexts and management options in this adversarial relation between the heart and the kidney, which exists in a substantial proportion of HF patients. Angiotensin converting enzyme inhibitors and β -blockers are associated with similar reductions in mortality in patients with and without renal insufficiency but usually are less often prescribed in patients with renal insufficiency. Careful monitoring of side effects and renal function should be done in all patients with renal insufficiency and prompt measures should be adopted to prevent further complications.

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INTRODUCTION

Heart failure (HF) is the fastest growing cardiovascular diagnosis in the United States. The prevalence of symptomatic HF is approximately 2% in adults with an age greater than 45 years^[1]. The annual incidence of HF is nearly 10 cases/1000 in patients ≥ 65 years and the life time risk of developing HF is estimated to be 20%^[2]. Chronic kidney disease (CKD) is present in 10% of the general population and is recognized as one of the major risk factors for cardiovascular disease. Renal function is a dynamic process that may worsen or improve in relatively short periods of time, and is an under-appreciated prognostic factor in HF. Furthermore, renal insufficiency is commonly viewed as a relative contraindication to some proven HF therapies^[3]. Renal dysfunction is common in HF patients with studies showing that stage III CKD; i.e. an estimated glomerular filtration rate (eGFR) of 60 mL/min per 1.73 m² or less, is present in 35%-50% of HF patients^[4].

In the last two decades, successful development of a number of therapies such as angiotensin converting

enzyme inhibitors, angiotensin receptor blockers (ARB), β blockers, aldosterone antagonists, implantable cardioverter defibrillators and cardiac resynchronization therapy have all been shown to reduce mortality and morbidity among patients with stable systolic HF in large, prospective randomized trials. However, patients with marked impairment of renal function were generally excluded from these studies.

The prospective outcomes study in heart failure^[5] showed that the presence of worsening renal function [defined as an increase in serum creatinine ≥ 26 $\mu\text{mol/L}$ (0.5 mg/dL) from admission value] in decompensated HF was associated with longer duration of hospital stay (median of 11 d, $P = 0.006$). A sub-analysis of the candesartan in HF: assessment of reduction in morbidity and mortality database^[6] revealed that the risk of cardiovascular death or hospitalization for worsening HF was significantly increased in subjects with eGFR less than 60 mL/min per 1.73 m², with an adjusted hazard ratio of 1.54 for patients with eGFR of 45-60 mL/min per 1.73 m² and 1.86 for those with eGFR < 45 mL/min per 1.73 m² ($P < 0.001$).

PATHOPHYSIOLOGIC CHANGES IN CKD AND HF

The relationship between the CKD and HF is an interdependent process, with impaired renal function increasing the risk of HF^[7]. The neurohormonal response associated with both heart and renal failure has been proposed as a key link between the two syndromes and has the capability of amplifying both disease processes^[8]. On the one hand, activation of the renin-angiotensin-aldosterone system and sympathetic nervous system promotes deleterious myocardial remodeling and accelerated atherosclerosis leading to increased prevalence of HF, coronary artery disease, stroke and peripheral arterial disease. On the other hand, neurohormonal activation induces renal vasoconstriction, intraglomerular hypertension, glomerulonecrosis and tubulointerstitial fibrosis leading to progressive kidney disease. This mutual interaction triggers a vicious circle in which renal insufficiency alters cardiac performance, which in turn leads to further impairment of renal function. For example, a recent study by Damman *et al*^[9] showed that renal blood flow and vascular congestion are major determinants of GFR in patients with cardiac dysfunction.

B-TYPE NATRIURETIC PEPTIDE VALUES AND CKD

B-type natriuretic peptide (BNP) is produced by ventricular myocytes, is released in response to muscle stretch and is a useful marker in HF diagnosis and treatment^[10]. Normal BNP has a high negative predictive value, effectively excluding HF in both dialysis and non dialysis patients with CKD. Specificity of BNP is lower at all stages of renal impairment.

BNP may be affected by left ventricular hypertrophy (LVH) in patients with chronic renal disease. One study showed that in stable CKD patients, BNP values were elevated only in those with coexistent LVH^[11]. The role of BNP values in assessing volume overload in CKD patients is less clear than in patients with normal renal function. High atrial pressures, high aortic pressure and increased ventricular mass are common in CKD patients and have been associated with an increased BNP concentration. Additionally, BNP may be elevated secondarily to decreased renal filtration or decreased clearance by the kidneys. Thus, BNP values may be elevated in patients with renal dysfunction, even in the absence of clinically significant HF^[12]. BNP values may still be a useful test for diagnosing HF in the presence of CKD; however, this would require an appropriate upward adjustment of reference ranges.

DIALYSIS PATIENTS AND HF

HF is present in more than one third of dialysis patients^[13] with an incidence of 71 per 1000 person-years. For most patients, dialysis is performed 2-3 times per wk, and body water accumulates and fluctuates in between dialysis sessions, which plays a critical role in the development of LVH, which in turn predisposes to CHF^[14]. Records from the US renal data system^[15] have shown that hemodialysis is an independent risk factor for the development of HF with a 2 years mortality as high as 51%. In addition, a significant percentage of cardiac mortality is due to sudden death which appears to be temporally related to the dialysis procedure. A prospective study of hemodialysis patients identified older age, anemia, hypoalbuminemia, hypertension and systolic dysfunction as risk factors for the development of HF in dialysis patients^[16].

MANAGEMENT OF HF IN PATIENTS WITH CKD

The co-existence of CKD and HF has major clinical implications as baseline renal function is a strong determinant of outcome in patients with HF. Moreover, renal function is an important factor in the management of HF as it alters the pharmacokinetics and pharmacodynamics of several cardiovascular medications, necessitating drug dose adjustments. Conversely, certain cardiovascular medications can interfere with renal function and, hence, must be administered with caution in patients with underlying CKD.

Because patients with CKD have been relatively underrepresented in HF clinical trials, evidence based management of patients with concomitant CKD and HF is limited^[17]. Therefore, treatment strategies in such patients, including those described in this review, are based mainly on results of observational data from unselected cohorts, or from post-hoc analysis of clinical trials in which patient sub-groups with renal dysfunction were included.

Diuretics

Diuretics have a major clinical role in reducing fluid overload in patients with chronic HF and pulmonary congestion^[18]. The selection of the type of diuretic and dosage depend on both the level of glomerular filtration rate and the degree of fluid overload. Loop diuretics should be used as first-line agents in patients with a glomerular filtration rate of less than 30 mL/min per 1.73 m², because thiazide diuretics are relatively ineffective in these patients when used alone^[19]. A number of strategies can improve loop diuretic responsiveness in chronic HF patients with renal insufficiency^[20]. Salt intake should be reduced to no more than 2 g daily. The dosage of the loop diuretic should be progressively increased (to reach appropriate levels of the drug in the tubular site of action) until the effective dose is reached. Intravenous bolus administration is often more effective than an equivalent oral dose, because bypassing the gastrointestinal tract overcomes impaired drug absorption due to gut edema seen in advanced HF. The effective oral or intravenous dose of loop diuretics should be administered as often as needed to maintain the response. If, despite the above measures, diuretic resistance still persists, sequential blockade of sodium reabsorption in the nephron can be instituted by administering a distal-acting diuretic, such as hydrochlorothiazide or metolazone, along with a loop diuretic in a dose determined according to the patient's renal function.

Continuous intravenous infusion of diuretics may be more effective in resistant cases. This process, by maintaining a constant rate of drug excretion, prevents the post-diuretic salt retention associated with sequential doses^[21].

Combination diuretic therapy requires close monitoring because it carries a considerable risk of adverse effects including a significant decrease in renal function, hypovolemia, hypokalemia and hyponatremia.

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme (ACE) inhibitors are the cornerstone of HF therapy and improve survival in patients with HF and left ventricular dysfunction. Studies have shown the efficacy of ACE inhibitors in all symptomatic classes of systolic HF patients^[22]. The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)^[23], a trial of ACE inhibitor vs. placebo in patients with severe HF, included the highest proportion of patients with renal insufficiency among published ACE inhibitor trials. The stated enrollment criteria for CONSENSUS excluded patients with a serum creatinine level greater than 300 µmol/L (3.4 mg/dL); however, only 26 of 253 participants had a serum creatinine level greater than 175 µmol/L (2.0 mg/dL) and none had a serum creatinine level greater than 250 µmol/L (2.8 mg/dL). The median serum creatinine level was 123 µmol/L (1.4 mg/dL), and the mean estimated GFR was 45 mL/min per 1.73 m², indicating moderate renal insufficiency on average. Participants assigned to the enalapril group of the study had 31% lower mortality at

1 year, and those with baseline serum creatinine levels greater than and less than the median had similar survival benefit^[24]. However, the study did not include many patients with severe renal insufficiency (estimated GFR < 30 mL/min per 1.73 m²); hence the tradeoff between efficacy and safety of ACE inhibitors in these patients remains unknown. Careful use of ACE inhibitors should be attempted in patients with severe renal insufficiency because of the potential to improve survival; however, many patients will not tolerate these agents because of hyperkalemia and worsened renal function.

A meta-analysis of five randomized trials of ACE inhibitor therapy in patients with HF showed that although the proportion of patients who developed renal dysfunction was higher in the ACE inhibitor groups than in the placebo groups, drug discontinuation was required in only a small percentage of patients, and renal function returned to baseline in most patients even without dose adjustment^[25]. A retrospective analysis of the studies of left ventricular dysfunction (SOLVD) has shown that the use of ACE inhibitors was associated with a reduced risk of mortality, even at moderately and severely depressed levels of glomerular filtration rate, and did not have an adverse impact on kidney function^[26]. Therefore, in patients with chronic HF, mild-to-moderate renal insufficiency should not be viewed as a contraindication to ACE inhibitor therapy, and a mild and nonprogressive worsening of renal function during initiation of therapy should not be considered an indication to discontinue treatment, as the drug may offer the dual benefit of reducing disease progression in both the heart and the kidney^[27]. In patients with moderate or severe renal insufficiency, therapy with low doses of ACE inhibitors should be initiated and the dose should be increased gradually with careful monitoring of renal function and serum electrolytes^[28]. When the initiation of ACE inhibitor therapy leads to an increase in serum creatinine levels of more than 30% above baseline, several strategies have been suggested^[29]. First, ACE inhibitors should be discontinued, and the patients should be evaluated for conditions causing renal hypoperfusion in which the use of ACE inhibitors may result in acute renal failure, such as excessive depletion of circulating volume due to intensive diuretic treatment, concurrent administration of vasoconstrictor agents [most commonly, nonsteroidal anti-inflammatory drugs (NSAIDs)] and severe bilateral renal artery stenosis. Unless renal vascular disease is present, therapy with an ACE inhibitor can be reinstituted after correction of the underlying cause of reduced renal perfusion^[30]. The risk of hyperkalemia associated with the use of ACE inhibitors in patients with HF and renal dysfunction is also a source of concern. Several measures may be used to minimize the risk of hyperkalemia in such patients, including discontinuation of drugs known to interfere with renal potassium excretion (e.g. NSAIDs, including cyclooxygenase-2 inhibitors), administration of a low potassium diet, as well as sodium bicarbonate in patients with metabolic acidosis^[31]. A potassium level

of ≥ 5.5 mEq/L should prompt a reduction in the ACE inhibitor dose.

Angiotensin II receptor blockers

There is evidence that angiotensin II is produced in the myocardium through alternative pathways independent of ACE that involve enzymes such as chymase, which are not blocked by ACE inhibitors^[32]. An augmented activity of these local pathways may lead to increased production of angiotensin II in patients with HF, and angiotensin II is a major adverse influence of cardiac remodeling and dysfunction.

The angiotensin II receptor blockers have been compared with ACE inhibitors regarding their effect on survival and renal complications in HF patients. Although the ELITE (Evaluation of Losartan in the Elderly) trial^[33] found a mortality benefit in favor of losartan compared with captopril, the larger ELITE-2 trial that followed did not confirm this finding; rather, it found no difference^[34]. Unfortunately, patients who experience hyperkalemia or worsened renal function while taking ACE inhibitors are likely to have the same complications with an ARB^[35]. Therefore, at present there are two settings in which angiotensin II receptor blockers might be used in HF: as an alternative in patients intolerant of ACE inhibitors due to cough, and in combination with ACE inhibitors in patients who remain severely symptomatic on conventional therapy^[36].

β -blockers

β -blockers counteract the harmful effects of sympathetic nervous system activation in HF^[37]. In addition to its antiarrhythmic properties and protection against sudden death, β blockade may also improve left ventricular remodeling and increase the left ventricular ejection fraction independent of the cause of HF. Therefore, β -blockers are recommended for all patients with stable mild, moderate or severe HF who are on standard treatment including diuretics and ACE inhibitors^[38]. The efficacy of β blockers in HF is not influenced by a reduction in glomerular filtration rate. In a retrospective analysis of the Cardiac Insufficiency Bisoprolol Study II^[39], as well as in several nonrandomized prospective investigations^[40,41], the favorable effects of β -blocking therapy on total mortality and rate of hospitalization did not differ in patients with and without moderate or severe renal insufficiency. In the SOLVD study, treatment with β -blockers was associated with a 30% decrease in the risk of worsening renal function, both in the ACE inhibitor and the placebo groups^[42]. Because metoprolol and carvedilol are predominantly cleared by the liver, these agents may be safer in patients with renal insufficiency^[43].

Spirolactone

High levels of aldosterone have deleterious effects on the heart by promoting the development of cardiac hypertrophy and fibrosis, as well as by contributing to the development of arrhythmias. In patients with HF, aldo-

sterone antagonists counteract these negative effects^[44]. In the Randomized Aldactone Evaluation Study (RALES), spironolactone reduced mortality by 30% in patients with severe HF^[45]. The RALES investigators excluded patients with a serum creatinine level of 221 $\mu\text{mol/L}$ (2.5 mg/dL) or greater; the median creatinine level in enrolled subjects was 106 $\mu\text{mol/L}$ (1.2 mg/dL). A significant treatment benefit was observed in patients with creatinine levels greater than and less than the median. Only 2% of patients assigned to spironolactone in RALES experienced serious hyperkalemia, and the study did not report an association of renal function with hyperkalemia. Patients in RALES, however, were treated with an average furosemide dose of 80 mg, which may have limited the incidence of hyperkalemia. The proportions of patients in RALES with an estimated GFR less than 30 mL/min per 1.73 m² and 30-60 mL/min per 1.73 m² have not been published. Thus, spironolactone should not be used in HF patients whose GFR is less than 30 mL/min per 1.73 m² and should be used cautiously in patients with an eGFR of 30-60 mL/min per 1.73 m², at a dosage no higher than 25 mg/d.

Digoxin

The clearance of digoxin varies linearly with GFR; hence, renal function may affect the safety profile of digoxin^[46]. No studies have evaluated whether the effect of digoxin on clinical outcomes is influenced by renal function. The Digitalis Investigation Group (DIG) trial evaluated the efficacy of digoxin in a double blinded placebo controlled manner^[47]. An exclusion criterion in the DIG trial was a serum creatinine level greater than 265 $\mu\text{mol/L}$ (3.0 mg/dL), and the median creatinine levels were 115 $\mu\text{mol/L}$ (1.3 mg/dL) in males and 97 $\mu\text{mol/L}$ (1.1 mg/dL) in females. Overall, digoxin did not affect survival but led to a 28% reduction in HF hospitalizations. To be used safely in patients with HF and renal insufficiency, digoxin therapy should be initiated without a loading dose and maintained at a low dose (0.125 mg), perhaps on alternating days and serum digoxin levels should be monitored to maintain a serum concentration in the acceptable range of 0.5-1.0 ng/mL^[48], and patients should be monitored carefully for symptoms and signs of digoxin toxicity.

CONCLUSION

CKD is common among patients with HF and is independently associated with an increased morbidity and mortality in this population. Treating patients with HF and kidney disease requires careful balancing of risk to benefit ratio of therapeutic agents. Rather than relying on serum creatinine levels, clinicians should estimate GFR to categorize renal function. The available data indicate that ACE inhibitors offer a survival advantage in patients with HF with mild and moderate renal insufficiency; however, their use in patients with severe renal insufficiency requires caution because of the potential

risk for adverse events. The effect of β -blockers on improving HF survival is less likely to be affected by renal function. Diuretic doses should be adjusted in patients with renal failure with careful monitoring of side effects, including worsening renal function. Aldosterone inhibitors, although associated with improved survival, should be used with great caution in patients, and only in those with mild renal dysfunction.

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Acoustic cardiography to improve detection of coronary artery disease with stress testing

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Abstract

AIM: To assess if performance of 12-lead exercise tolerance testing (ETT) can be improved by simultaneous acoustic cardiography and to compare the diagnostic performances of electrocardiography (ECG) during ETT and acoustic cardiography for detection or exclusion of angiographically proven coronary artery disease (CAD).

METHODS: We conducted an explorative study with retrospective data analysis using a convenience sample of consecutive patients ($n = 59$, mean age: 62 years) from an outpatient clinic in Switzerland, who were referred for ETT by their general practitioner on suspicion of CAD, and in whom, coronary angiography was carried out. Measurements included sensitivity, specificity, likelihood ratios and receiver operating characteristic curves. A standard, symptom-limited, 12-lead ECG exercise tolerance test was performed by independent persons with simultaneous acoustic cardiography and subsequent cardiac angiography for determination of significant CAD.

RESULTS: Thirty-four of the 59 adult subjects (58%) had a final diagnosis of CAD by angiography, and in 25 subjects, CAD was excluded by angiography. Sensitivity/specificity of ST segment depression in the group

was 29%/92%, whereas the most powerful acoustic cardiographic parameter was the strength of the fourth heart sound (S₄), with corresponding sensitivity/specificity of 53%/92%. The disjunctive combination of the S₄ and ST depression had sensitivity/specificity of 68%/84%.

CONCLUSION: In this preliminary pilot study, the use of acoustic cardiography alone during ETT or disjunctively with ST depression has been shown to be a simple and convenient method for the detection of CAD, which was superior to ST depression on the standardized ECG.

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Key words: Heart sounds; Electrocardiography; Stress testing; Coronary artery disease; Acoustic cardiography

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INTRODUCTION

The standard 12-lead electrocardiography (ECG) exercise tolerance or stress test is a commonly used procedure for detecting the presence of coronary artery disease (CAD). The diagnostic accuracy of the 12-lead ECG exercise test has important limitations, including the confounding presence of left ventricular hypertrophy and reduced performance in women^[1,2]. To improve the diagnostic accuracy of the exercise tolerance test, it is useful to use diagnostic parameters in addition to ST segment

displacement. Therefore, the exercise tolerance test is often performed in conjunction with echocardiographic or radionuclide studies. These additional tests provide independent diagnostic data that are used to augment the interpretation of the exercise tolerance test^[3-5]. However, due to the specialized equipment and personnel involved, echocardiographic and radionuclide studies are expensive and often not readily available. This is especially important since the exercise tolerance test is employed as a screening test in large patient populations.

Acoustic cardiography is a technique that records simultaneous digital ECG and heart sound data and provides computerized interpretation of the findings. It does this by using dual-purpose ECG and sound sensors that are applied to the patient's thorax in the V3 and V4 position. The rationale for using this diagnostic technique during exercise testing is that ischemia not only alters the electrical properties of myocardial cells, but also affects the mechanical properties of the ventricle. For example, acute left ventricular ischemia reduces the compliance of the left ventricular chamber and often leads to the production of a fourth heart sound (S4)^[6-9]. Therefore, we evaluated the usefulness of acoustic cardiography during stress testing as a single and additive measurement for the detection of angiographically proven CAD.

MATERIALS AND METHODS

Design overview

Consecutive patients with clinically suspected CAD who were referred for standard ECG exercise tolerance testing (ETT) were enrolled after providing informed consent. The study protocol was approved by the local medical ethics committee. If deemed appropriate by the physician performing the exercise tolerance test, the patient was then sent for a diagnostic cardiac catheterization procedure to determine the presence and extent of CAD. The physicians performing the exercise tolerance test and the catheterization were blinded to the results of the other diagnostic procedure.

Setting and participants

The exercise tolerance test and cardiac catheterization were performed in an outpatient facility in an urban setting in Switzerland. We enrolled 59 subjects with clinically suspected CAD in the study for ETT. All patients (40 men and 19 women, mean age 62 years, all Caucasian) underwent both coronary angiography and ETT with adequate ECG and acoustic cardiography. Acoustic cardiographic equipment was provided by Inovise Medical, Inc. (Portland, OR, USA) through an equipment loan program.

Randomization and interventions

ETT protocol: All subjects underwent symptom-limited stress testing using an upright bicycle ergometer. The workload of each exercise tolerance test began at 50 W and was increased at a rate of 20 W/min in men and

15 W/min in women. The test was terminated when either symptoms or a silent but diagnostic ST depression occurred. Medical therapy was not stopped or modified prior to ETT. ST depression was measured in all 12 ECG leads and a test was considered ECG-positive if there was exercise-induced horizontal or down-sloping ST depression $> 100 \mu\text{V}$ in any of the limb leads, or $> 200 \mu\text{V}$ in any of the chest leads. In each case, we measured the maximum ST segment displacement at a point 60 ms beyond the J point. ST segment displacement was measured digitally using a computerized ECG algorithm (Schiller AG, Baar, Switzerland).

Cardiac catheterization: Coronary angiography and left ventriculography were performed under light sedation in the post-absorptive state using standard techniques. Left ventricular end-diastolic pressure was recorded, left ventriculography was performed in the right anterior oblique projection, and coronary angiograms were obtained in multiple projections. CAD was considered to be present if there was a $> 70\%$ reduction in the transluminal diameter of at least one major coronary artery. In each case, ETT and cardiac catheterization were performed within 2 mo of each other.

Acoustic cardiography: In addition to the 12-lead ECG data, simultaneous acoustic cardiographic data were recorded (A200; Inovise Medical Inc.). For the purpose of the present study, we chose evidence of an exercise-related S4 as an indicator of underlying CAD. Acoustic cardiography obtained evidence of S4 by searching for discrete sounds in a frequency range of 60-180 Hz that occurred in the interval between the onset of the ECG P wave and the first heart sound. The intensity of such sounds was expressed as a continuous parameter on a scale of 0 to 10. The strength of evidence for an S4 was proportional to the value of this intensity and its persistence during the recording. The heart sound data collection, analysis and calculation of parameter values were fully automated and independent of the user. Follow-up was not performed on these subjects.

Statistical analysis

Data are presented as mean values and SD for continuous variables with normal Gaussian distribution. We analyzed the ST segment depression and the S4 strength data that were obtained at maximum heart rate for each subject. For the entire group, for the male and female subgroups, and for the symptomatic and silent ischemic patients, we determined the sensitivities and specificities of the above ST segment criteria for CAD. We then used receiver operating characteristic curves to determine the sensitivities of the S4 measurements at specificities similar to those exhibited by the ST segment criteria. Confidence intervals were calculated at the 95% level. Positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were calculated using standard formulas. The analyses were performed using SPSS version 13.0

Table 1 Baseline clinical characteristics

	All (<i>n</i> = 59)	No CAD by angiography (<i>n</i> = 25)	CAD by angiography (<i>n</i> = 34)
Baseline characteristics			
Age (yr)	62 ± 11	61 ± 13	62 ± 10
History of angina	37 (63)	13 (52)	24 (71)
Echo ejection fraction (%)	59 ± 11	59 ± 7	59 ± 12
Invasive LV end-diastolic pressure (mmHg)	15 ± 7	14 ± 6	15 ± 8
Baseline heart rate (beats/min)	67 ± 12	66 ± 11	69 ± 13
Maximum heart rate during ETT (beats/min)	129 ± 19	137 ± 19	122 ± 17
Baseline ST depression	12 (20)	2 (8)	10 (29)
Maximum workload during ETT (W)	132 ± 41	149 ± 43	119 ± 34
Heart rate × SBP at rest (mmHg/min)	9357 ± 2397	8991 ± 2314	9634 ± 2457
Heart rate × SBP at peak exercise (mmHg/min)	25790 ± 5740	27870 ± 5070	24210 ± 5780
Rise in double pressure product (factor)	2.9 ± 0.9	3.3 ± 1.0	2.6 ± 0.7
Baseline SBP (mmHg)	138 ± 24	137 ± 22	140 ± 27
Maximum SBP during ETT (mmHg)	200 ± 28	203 ± 25	197 ± 29
Symptomatic ST depression (mm)	1.98 ± 0.55	NA	1.98 ± 0.55
Silent ST depression (mm)	2.05 ± 1.23	NA	2.05 ± 1.23
LBBB	1 (2)	0 (0)	1 (3)
RBBB	3 (5)	2 (8)	1 (3)
Acoustic cardiographic S3 detected	1 (2)	0 (0)	1 (3)
Acoustic cardiographic S4 detected	6 (10)	1 (4)	5 (14)
CAD risk factors			
High cholesterol (> 5.2 mmol/L)	41 (69)	18 (72)	23 (68)
Stage 1 blood pressure (SBP 140-159, DBP 90-99 mmHg)	18 (30)	7 (28)	11 (32)
Stage 2 blood pressure (SBP > 160, DBP > 100 mmHg)	14 (24)	5 (20)	9 (26)
Diabetes (fasting glucose > 6.1)	5 (8)	2 (8)	3 (9)
Body mass index (kg/m ²)			
Overweight (25-29.9)	29 (49)	11 (44)	18 (53)
Obese (> 30)	14 (24)	5 (20)	9 (26)
Age (men > 45 yr, women > 55 yr)	41 (69)	17 (68)	24 (71)
Prior myocardial infarction	13 (22)	5 (20)	8 (23)

Values are given either as mean ± SD for continuous parameters or as *n* (percentage) for dichotomous variables. Prior myocardial infarction based on medical history, echocardiography or angiography. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; NA: Not applicable; CAD: Coronary artery disease; ETT: Exercise tolerance testing; LBBB: Left bundle branch block; RBBB: Right bundle branch block; LV: Left ventricular.

Table 2 Medical therapy in patients with and without CAD by angiography

Condition	All (<i>n</i> = 59)	No CAD by angiography (<i>n</i> = 25)	CAD by angiography (<i>n</i> = 34)
Hyperlipidemia	23 (70)	7 (86)	16 (62.5)
Hypertension	30 (87)	12 (92)	18 (83)
Diabetes	5 (20)	2 (0)	3 (33)

Values are given as *n* (percentage) of the group being treated with drug therapy.

(SPSS, Inc., Chicago, IL, USA) and Excel 2000 (Microsoft, Seattle, WA, USA).

RESULTS

Of the 59 subjects, 34 (58%) had CAD by angiography. Additional clinical findings of the subjects are summarized in Table 1, including accepted risk factors for CAD. All patients were in sinus rhythm, one subject had left bundle branch block, and three had right bundle branch block. The medical therapy being received by these sub-

Table 3 Extent of angiographic CAD

	All (<i>n</i> = 34)	S4 at Max HR (<i>n</i> = 18)	ST depression (<i>n</i> = 10)	S4 or ST depression (<i>n</i> = 23)
Left main artery	2 (6)	1 (6)	1 (10)	2 (9)
Left anterior descending	24 (71)	15 (83)	8 (80)	20 (87)
Right circumflex artery	17 (50)	10 (56)	7 (70)	13 (57)
Right coronary artery	24 (71)	10 (56)	6 (60)	13 (57)
One-vessel disease	13 (38)	7 (39)	3 (30)	8 (35)
Two-vessel disease	10 (29)	5 (28)	2 (20)	6 (26)
Three-vessel disease	11 (32)	6 (33)	5 (50)	9 (39)
Invasive ejection fraction (%)	65 ± 11	67 ± 11	70 ± 12	67 ± 11
Invasive LVEDP (mmHg)	15 ± 8	18 ± 9	11 ± 8	15 ± 9

Values are given either as mean ± SD for continuous parameters or as *n* (percentage) for dichotomous variables.

jects is presented in Table 2, and Table 3 describes the angiographic findings in those patients with CAD. Note that, in the whole group, there were equal proportions of subjects with one-, two- and three-vessel disease, and

Table 4 Diagnostic performances of ECG versus heart sounds in 59 patients (40 men, 19 women)

Parameter	Group	Sensitivity (%)	Specificity (%)	PLR	NLR
ST depression	All	29 (CI 17-46)	92 (CI 75-98)	3.68 (CI 0.88-15.3)	0.77 (CI 0.60-0.98)
ST depression	Men	28 (CI 14-48)	93 (CI 70-99)	4.2 (CI 0.57-30.9)	0.77 (CI 0.58-1.02)
ST depression	Women	33 (CI 12-65)	90 (CI 60-98)	3.33 (CI 0.42-26.58)	0.74 (CI 0.45-1.23)
S4 present	All	53 (CI 37-69)	92 (CI 75-98)	6.62 (CI 1.7-25.9)	0.51 (CI 0.35-0.74)
S4 present	Men	52 (CI 34-70)	93 (CI 70-99)	7.8 (CI 1.13-53.8)	0.51 (CI 0.34-0.79)
S4 present	Women	56 (CI 27-81)	90 (CI 60-98)	5.56 (CI 0.79-39.01)	0.49 (CI 0.23-1.06)
S4 or ST-depression	All	68 (CI 51-81)	84 (CI 65-94)	4.23 (CI 1.7-10.7)	0.39 (CI 0.23-0.65)

PLR: Positive likelihood ratio; NLR: Negative likelihood ratio.

that the right coronary artery and the left anterior descending artery had a similar prevalence of disease.

Table 4 shows a comparison of the diagnostic performances of the ECG and of the acoustic cardiographic findings. The data revealed that, in these subjects, the specificities of the ST segment and the S4 criteria exceeded 90% in the entire group and in the male and female subgroups, but with poor sensitivities (28%-33%). The table also shows that, at these specificities, the sensitivities of the acoustic cardiographic S4 at maximum heart rate as a single parameter exceeded the corresponding sensitivities of the ST segment criteria by 24%, 24% and 23%, respectively. In the entire group and in both subgroups, the value of S4 strength that was associated with these diagnostic performances was 3.6. The disjunctive combination of the ST segment and the S4 had sensitivity/specificity of 68%/84%. Although the disjunctive combination had improved sensitivity, both the PLR and NLR were higher for the S4 at maximum heart rate alone.

Figure 1 shows the heart rate and S4 strength trends during ETT for a patient with CAD by angiography and one without CAD by angiography.

DISCUSSION

This study confirms the limited sensitivity (Table 4, 28%-33%) of using standard ST depression criteria during a 12-lead ECG ETT, even with an intermediate pretest probability for CAD, since a majority of our patients had ≥ 2 multiple risk factors. At similar specificity, the acoustic cardiographic S4 provided improved sensitivity (52%-56%) for detection of angiographically proven CAD. The disjunctive combination of ECG or the S4 resulted in modest improvement sensitivity (68%) at the expense of reduced specificity (84%) over just the presence of S4 alone.

Although the ECG-based exercise tolerance test remains a widely used technique for detecting underlying CAD, it has been shown that its diagnostic accuracy is suboptimal^[3-5,10-12]. The reasons for this include variations in the prevalence of heart disease in the patients tested and inadequate levels of exercise performance^[10,11]. In addition, the presence of pre-existing ECG abnormalities, e.g. left ventricular enlargement or left bundle branch block is particularly problematic for diagnosing ischemia using the ST segments. This has remained the case even

when parameters such as the ST segment/heart rate slope or ST segment/heart rate index are substituted for the simple measurement of ST segment displacement^[10-12]. Typical angina during stress has a high prognostic value for the detection of CAD. In our population, the percentages of patients with symptomatic *vs* asymptomatic ischemia were similar in patients with ST depression (60% symptomatic *vs* 40% asymptomatic) or without ST depression (58% symptomatic *vs* 42% asymptomatic). However, even the detection of silent ischemia is important, because we have shown that it also has an impact on long-term follow-up^[13,14].

Therefore, echocardiographic and radionuclide studies such as single proton emission computed tomography are frequently used in conjunction with ETT^[3-5]. These tests provide orthogonal diagnostic information that is intended to augment the interpretation of associated ECG abnormalities. Their sensitivities/specificities range from 80% to 100%, depending on the extent of CAD^[15]. However, both exercise echocardiography and radionuclide stress tests are expensive and not always available in offices and clinics in which screening for CAD is desirable. In contrast, acoustic cardiography is easy to perform and requires the addition of two dual-purpose sensors. Furthermore, it requires no expertise in the interpretation of cardiac acoustic data, because the analysis of the ECG and heart sound data is computerized. Therefore, this test could be interesting for general practitioners and outpatient medicine outside the hospital.

Previous studies have shown the clinical value of various acoustic cardiographic parameters^[16-22]. In the present study, we chose to evaluate the S4 heart sound at maximum heart rate, because of the well-recognized association between acute myocardial ischemia and diastolic dysfunction as an early sign in the ischemic cascade^[23-28]. This association is due to the abrupt decrease in left ventricular compliance that occurs with the onset of ischemia^[6-9]. Figure 1A illustrates heart rate and S4 strength for a subject without CAD by angiography. The decrease in S4 strength may be explained by a vagal response and decrease in left ventricular volume and filling pressures. Figure 1B presents the heart rate and S4 strength trends during ETT in a patient with CAD by angiography. The S4 strength increased as ventricular stiffness increased with ischemia and a rise in left ventricular filling pressure.

Although auscultation has traditionally been used to

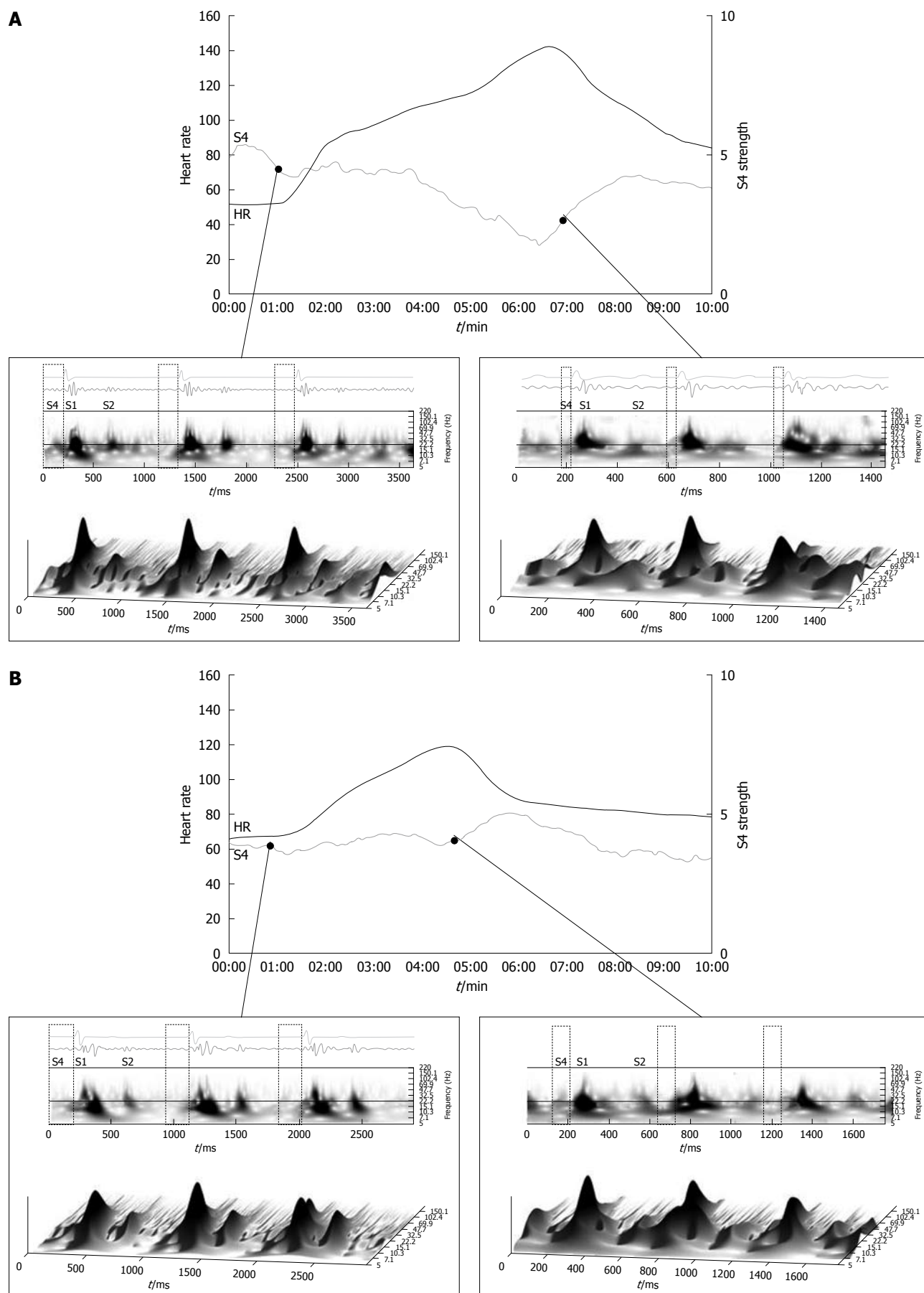


Figure 1 Heart rate and S4 strength trends during exercise tolerance testing (ETT). A: A patient without coronary artery disease (CAD) by angiography; B: A patient with CAD by angiography.

detect S4, the low frequency and intensity of this sound often make it difficult to hear. The ability of the acoustic cardiography system to amplify the recorded sounds and determine their frequencies makes S4 detection more reliable than it is with auscultation. Also, acoustic cardiography provides an automated interpretation of the diagnostic findings so that a high level of skill in either heart sound detection or ECG interpretation is not required^[29].

The findings of the present pilot study showed that, at similar diagnostic specificities, the sensitivities of the exercise-related S4 exceeded those of exercise-related ST segment depression for detecting CAD. These differences are especially important, because exercise testing is typically used as a screening test for CAD in large numbers of patients. For example, ST depression detected 10 of the 34 patients with CAD, whereas the S4 at maximum heart rate diagnosed 18 patients. Extrapolating the data shown in Table 4 to a hypothetical population of 100 women with CAD, the use of S4 detected using acoustic cardiography alone would produce 23 additional true positive test results, compared with ECG alone. Although the disjunctive combination of S4 at maximum heart rate and ST depression had better sensitivity than S4 alone, both the PLR and NLR were better with S4 alone (PLR 6.62 and NLR 0.51 for S4 alone *vs* PLR 4.23 and NLR 0.39 for the disjunctive combination). Therefore, we would like to recommend the measurement of S4 at maximum heart rate for the detection of CAD during exercise testing. Also, as indicated by Erne^[30], the use of acoustic cardiography during 24-h Holter monitoring may provide a way to detect silent ischemia during routine activities. In the present study, S4 at maximum heart rate detected 67% of the patients with CAD and silent ischemia.

For a pilot study, the number of subjects was small. In particular, the number of subjects without CAD by angiography was limited and had an impact on our results. Although we included no other tests at the termination of exercise, we verified CAD with coronary angiography in all of the patients included in this analysis. Potential bias towards higher sensitivity and lower specificity for the ECG stress test results existed, since those test results were the primary input for the decision as to which patients to refer for angiographic evaluation. Since the number of patients was small, the results shown in the subgroup analysis are not likely to be statistically relevant.

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COMMENTS

Background

The performance of standard 12-lead electrocardiography (ECG) exercise tolerance or stress test is well characterized, and it is understood that this has deficiencies with respect to sensitivity and specificity for the detection of coronary artery disease (CAD).

Research frontiers

Not much is known about the utility of quantified heart sounds to improve the performance of ECG stress tests for diagnosis of CAD.

Innovations and breakthroughs

For the first time, this article evaluates the utility and performance of computerized and quantitative heart sound analysis to improve the performance of ECG stress tests for the detection of CAD.

Peer review

This is an original editorial about stress testing and acoustic cardiography. But it must be made major revision.

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Efficacy and safety of valsartan plus hydrochlorothiazide for high blood pressure

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Abstract

AIM: To evaluate efficacy and tolerability of the combination valsartan plus hydrochlorothiazide (160 mg and 25 mg daily, respectively) in young-middle aged males with high-normal blood pressure (BP) or first-degree arterial hypertension with evidence of target organ damage.

METHODS: Twenty males with high-normal BP or first-degree hypertension associated with left ventricular concentric remodeling and/or increased aortic stiffness were enrolled. BP at rest and during exercise, and echocardiographic parameters of the left ventricle (LV), were evaluated at baseline and after 3 mo of treatment. The effects of treatment on aortic stiffness, metabolic parameters, renal and erectile function were also assessed.

RESULTS: BP was significantly reduced by treatment both at rest ($P < 0.001$) and during exercise ($P < 0.001$), and 85% of patients achieved BP normalization ($< 130/85$ mmHg). Doppler echocardiography showed a significant reduction of LV mass ($P < 0.005$). LV hypertrophy was identified in 70% of subjects at baseline and in 5% after 3 mo of treatment. The ratio of early (E) to late (A) trans-mitral diastolic flow velocity increased, ($P < 0.05$), the relative wall thickness decreased ($P < 0.05$) and the left ventricular relaxation time shortened ($P < 0.005$). The left atrial diameter ($P < 0.05$) and the aortic diameter ($P < 0.05$) and stiffness ($P < 0.005$) also decreased.

CONCLUSION: The full-dose combination of valsartan plus hydrochlorothiazide produced optimal BP control with regression of target organ damage, already after 3 mo, without relevant side effects.

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Key words: Hypertension; Valsartan and hydrochlorothiazide; Cardiac remodeling; Aortic stiffness

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INTRODUCTION

Hypertension is one of the most prevalent cardiovascu-

lar risk factors in the adult population and is therefore considered an important medical and public health issue^[1,2]. Both blood pressure (BP) values and duration of hypertension influence the level of risk for stroke, heart failure, atherosclerosis, heart attack and kidney disease^[3,4]. In the new European Guidelines, hypertension is defined by a systolic BP (SBP) of > 139 mmHg and/or diastolic BP (DBP) of > 89 mmHg. To reduce cardiovascular risk, the European Guidelines recommend prompt treatment of patients affected by hypertension^[5]. Moreover, longitudinal data from the Framingham Heart Study showed that subjects with a BP value of 130-139/85-89 mmHg have a more than twofold increase in the relative risk for cardiovascular diseases *vs* patients with BP ≤ 120/80 mmHg^[6-8]. Furthermore, it has been reported that about 50% of pre-hypertensive individuals (SBP 120-139 mmHg, DBP 80-89 mmHg) have an excessive BP increase during exercise compared with normotensive subjects and echocardiographic evidence of structural and functional abnormalities of the left ventricle (LV)^[9]. It is essential to identify these patients because, as with patients affected by mild hypertension, they are often under-treated despite their high cardiovascular risk and because they easily develop target organ damage and cardiovascular events in the mid to long term^[10]. According to the most recent European Guidelines, the treatment of elevated BP in the pre-hypertensive-first degree range depends not only on the values of BP but also on the presence of other risk factors such as age, smoking, diabetes, sedentary lifestyle and, particularly, the presence of target organ damage. In addition to lifestyle recommendations (i.e. low sodium diet, weight loss, limited alcohol intake, smoking cessation and aerobic exercise)^[11], there are now a wide range of drugs (i.e. diuretics, β -blockers, calcium-antagonists, ACE-inhibitors, and especially sartans) that may be used to treat arterial hypertension^[1]. However, despite the more stringent guidelines and the rich therapeutic arsenal, it is estimated that only 58% of hypertensive individuals receive treatment and among these only 31% maintain good BP control^[12]. This limited success is due to several factors, among which are the lack of diagnosis in many candidates in whom a pharmacologic treatment should be advised, inadequate treatment and poor compliance to pharmacologic therapies. Consequently, there is high incidence of cardiovascular events, morbidity, mortality and disability within the population, with significant increases in public spending.

Hypertension may be underrated also because it is not always possible to identify hypertensive subjects from the measurement of BP at rest alone. Indeed, many subjects may have normal BP at rest, but their pressure increases excessively during the psycho-physical stresses of everyday life^[13,14]. Furthermore, poor compliance of some patients may be due to unpleasant side effects of prescribed drugs. Among these, erectile dysfunction is one of the most frequent causes of therapy discontinu-

Table 1 Characteristics of the study population

Patients	20
Age (yr)	51 ± 9
Weight (kg)	77 ± 10.9
Body surface area (m ²)	1.8 ± 0.15
Body mass index (kg/m ²)	26.47 ± 2.9
Systolic blood pressure (mmHg)	141 ± 7
Diastolic blood pressure (mmHg)	89 ± 5.3
Left ventricular hypertrophy (%)	70

ity in male subjects^[15]. On these premises, the aim of this study was to demonstrate the efficacy and safety of a prompt pharmacologic treatment with the combination of valsartan plus hydrochlorothiazide in young-middle aged male subjects with slight hypertension and the presence of target organ damage.

MATERIALS AND METHODS

Patients

Twenty young or middle-aged males with first-degree hypertension or high-normal BP, and with echocardiographic evidence of LV concentric remodeling and/or high vascular stiffness, naïve for antihypertensive treatment, were selected from our outpatient department and enrolled in this prospective, not controlled, 12-wk study. Each patient provided written informed consent to the study. The protocol was approved by the Ethics Committee of our Medical School, and the study was carried out according to the principles outlined in the Declaration of Helsinki.

Inclusion criteria for recruitment were age between 18 and 60 years, high-normal BP (130-139/85-89 mmHg), essential first-degree hypertension (BP 140-159/90-99 mmHg), and echocardiographic evidence of left ventricular concentric remodeling and/or increased aortic stiffness. Exclusion criteria were documented presence of ischemic heart disease, kidney or endocrine failure, inability to perform the bicycle-ergometer test, diabetes mellitus and valvular heart disease or arrhythmias. The characteristics of the study population are reported in Table 1.

Patients consumed one tablet of the combination valsartan 160 mg plus hydrochlorothiazide 25 mg every morning for 3 mo.

Evaluations

At baseline (T0) and after 3 mo of treatment (T1) we measured patients' BP at rest in a sitting position and after a bicycle-ergometer test. This was performed by means of the version 5 CardioSoft software (General Electric, Freiburg, Germany), according to the Bruce Protocol. Each stage lasted 3 min, with progressive workload increments of 25 W^[16]. All patients performed exercise until reaching a workload of 100 W. This level of exercise was selected because it is considered comparable to that carried out during everyday life. BP was measured at the end of each stage^[9,17,18].

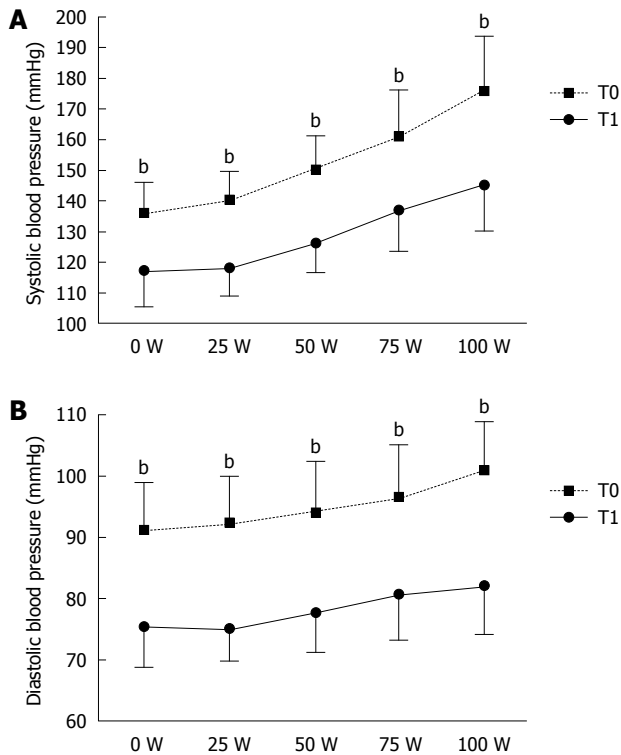


Figure 1 Exercise systolic (A) and diastolic (B) blood pressure profile before (T0) and after treatment (T1). ^b $P < 0.001$.

At T0 and T1, patients also underwent routine laboratory blood tests and transthoracic mono-two dimensional and Doppler echocardiography (i.e. pulsed wave, continuous wave and color Doppler) for the evaluation of morphological and functional cardiac parameters, according to the Guidelines of the American Society of Echocardiography^[19]. Echocardiographic examinations were carried out with a commercially available ultrasonograph (Aplo CV, Toshiba Co., Otawara, Japan) equipped with a 3-MHz linear transducer (PST-30BT). In particular, we measured left ventricular mass (g/m^2), relative wall thickness and the ratio of early (E) to late (A) trans-mitral diastolic flow velocity (E/A) and left ventricular relaxation time (msec) to evaluate left ventricular diastolic function. We also measured left atrial and aortic diameters (mm) and aortic stiffness (mmHg/mL), based on the pulse pressure/left ventricular stroke volume ratio^[20].

All patients were asked to complete the International Index of Erectile Function (IIEF-5) questionnaire, which assesses erectile function, at T0 and T1^[15]. The questionnaire consisted of five questions in the sexual sphere and a score was assigned to each item. The highest score possible was 25 and a score below 21 indicated erectile dysfunction.

Statistical analysis

Numeric variables are expressed as mean \pm SD. Data were analyzed with standard statistical software (SPSS 14.0 program). We used the two-tailed unpaired Student's

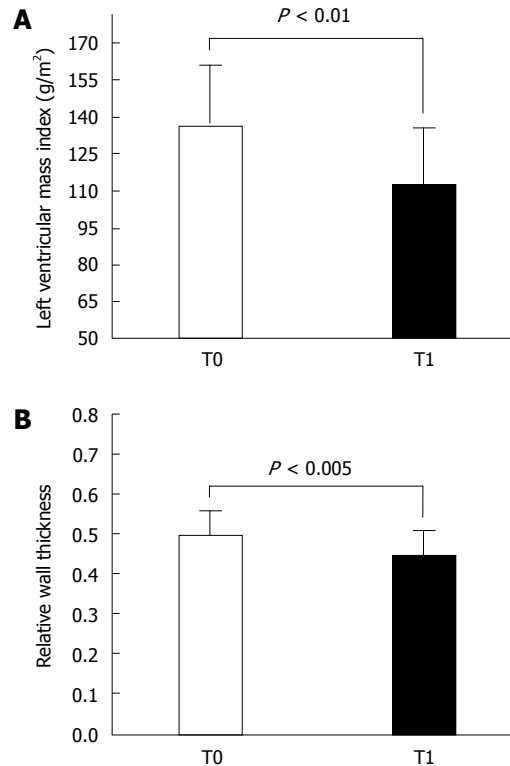


Figure 2 Significant reduction of left ventricular mass (A) and relative wall thickness (B) after 3 mo of treatment (T1) vs baseline (T0).

t -test and the χ^2 test for comparisons between mean values before and after treatment. A P value < 0.05 was considered statistically significant.

RESULTS

BP became normal ($\text{BP} < 130/85$ mmHg) in 85% of patients after 3 mo of treatment. In particular, rest BP values, both SBP and DBP, were significantly reduced after 3 mo of treatment: 141 ± 7 mmHg *vs* 116 ± 13 mmHg ($P < 0.001$) and 89 ± 5 mmHg *vs* 76 ± 7 mmHg ($P < 0.001$), respectively. In addition, treatment significantly reduced post-exercise SBP and DBP: 175 ± 16 mmHg *vs* 145 ± 15 mmHg ($P < 0.001$) and 101 ± 8 mmHg *vs* 82 ± 9 mmHg ($P < 0.001$), respectively (Figure 1).

The Doppler-echocardiographic results were equally impressive. Regarding morphological features, there was a significant reduction of left ventricular mass (136 ± 27 g/m^2 *vs* 112 ± 25 g/m^2 , $P < 0.005$) (Figure 2A) and relative wall thickness (0.49 ± 0.06 *vs* 0.44 ± 0.07 , $P < 0.05$) (Figure 2B). Furthermore, while concentric left ventricular hypertrophy was present in 70% of subjects at study entry, it was present in only 5% after 3 mo. Also, two diastolic functional parameters changed significantly: the E/A was increased (1.06 ± 0.32 *vs* 1.26 ± 0.36 , $P < 0.05$), while the left ventricular relaxation time was shorter (111 ± 20 ms *vs* 94 ± 15 ms, $P < 0.005$) (Figure 3A). Finally, we observed a reduction in the left atrial diameter (36 ± 4 mm *vs* 33 ± 4 mm, $P < 0.05$) and a reduction in the aortic diameter (36 ± 4 mm *vs* 34 ± 3.4 mm, $P < 0.05$) and stiff-

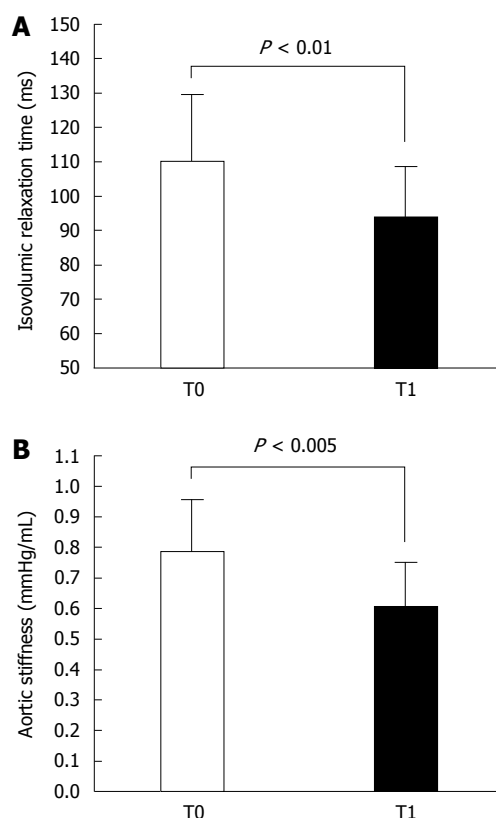


Figure 3 Significant shortening of isovolumetric relaxation time (A) and aortic stiffness (B) after 3 mo of treatment (T1) vs baseline (T0).

ness (0.78 ± 0.17 mmHg/mL *vs* 0.60 ± 0.15 mmHg/mL, $P < 0.005$) (Figure 3B).

No adverse effect resulted from treatment. In particular, metabolic parameters remained within normal values: low-density lipoprotein levels were 133 ± 28 mg/dL and 132 ± 25 mg/dL at T0 and T1, respectively, and fasting blood glucose levels were 90 ± 17 mg/dL and 90 ± 18 mg/dL at T0 and T1, respectively. Similarly, there were no significant changes in renal function or in the hydro-electrolytic balance.

Lastly, the IIEF-5 score showed that erectile function did not worsen after the combination treatment, the scores being 20.5 ± 3 at T0 and 21.4 ± 2 at T1.

DISCUSSION

The results of this study show that an early pharmacologic treatment with the combination valsartan plus hydrochlorothiazide (160 and 25 mg daily, respectively) in 20 young or middle-aged males with high-normal BP or first degree hypertension with evidence of target organ damage is very effective and well tolerated. Indeed, after 3 mo of treatment, BP was significantly reduced both at rest and during exercise and the proportion of patients reaching BP normalization (BP < 130/85 mmHg) was very high (85%).

Similarly, the treatment was very effective in counteracting target organ damage, thus highly reducing car-

diovascular risk. In particular, left ventricular mass and relative wall thickness were significantly reduced; concentric left ventricular hypertrophy was present in 70% of subjects at study entry and was present in only 5% after 3 mo of treatment. This was associated with a significant improvement in relaxation, as shown by the significant increase in trans-mitral E/A and the shortening of left ventricular relaxation time. In addition, there was a significant decrease in left atrial diameter and a reduction in aortic diameter and stiffness, as estimated by the pulse pressure/left ventricular stroke volume ratio. These impressive results obtained after only 3 mo of treatment could have important implications. In fact, as shown in this and previous studies, many subjects with only high-normal BP or first-degree hypertension may have increased left ventricular mass and concentric hypertrophy associated with diastolic dysfunction mainly due to impaired myocardial relaxation^[21,22]. Increased left ventricular mass is a recognized significant adverse prognostic factor^[23]. Furthermore, many of the patients included in this study also have increased aortic stiffness, which is another adverse prognostic factor^[24-26]. Consequently, a prompt pharmacologic intervention, which is able to normalize BP and correct these cardiovascular abnormalities, should reduce cardiovascular risk and improve the long-term prognosis even in the patients with high BP who are often untreated by the physician.

The striking results of this study were obtained without any metabolic side effects. In addition, the antihypertensive therapy used did not affect erectile function in our patients, with good compliance to treatment as derived by the tablet count and the results obtained. It is conceivable that the adverse effects that usually result from the administration of hydrochlorothiazide on metabolism and erectile function have been counteracted by the favorable effects of valsartan^[27,28]. After 12 mo of the same treatment, our 20 patients are stable and have not reported any adverse effects.

This study has some limitations. Optimal noninvasive assessment of diastolic ventricular function should be obtained with Tissue Doppler Imaging, because classic echocardiographic parameters may be influenced by several factors, such as afterload, ventricular filling and heart rate. Unfortunately, our echocardiographic equipment lacks the specific software to apply this technique. In the future, it would be useful to evaluate diastolic function in patients more accurately. Another limitation may be the small sample size and the open design; therefore a larger controlled study should be preformed to confirm our results.

Although a large, long-term, controlled study is needed to demonstrate whether this kind of therapeutic intervention could have a favorable prognostic impact, in our group of male patients with high BP, the early administration of full dose combination valsartan plus hydrochlorothiazide produced good control of BP and, after only 3 mo, a regression of cardiac and aortic ab-

normalities with improved left ventricular relaxation and aortic stiffness without any relevant side effect.

ACKNOWLEDGMENTS

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COMMENTS

Background

Notwithstanding the stringent guidelines and the rich therapeutic arsenal, it is estimated that only 58% of hypertensive individuals receive treatment and, among these, only 31% maintain good blood pressure (BP) control. This limited success is due to several reasons among which the lack of diagnosis in many candidates in whom a pharmacologic treatment should be advised, inadequate treatment and poor compliance to pharmacologic therapies are certainly important. Consequently, there is high incidence of cardiovascular events, morbidity, mortality and disability of the population, with significant increase in public spending. Furthermore, the poor compliance of some patients with the prescribed drugs may be due to unpleasant side effects. Among these, erectile dysfunction is one of the most frequent causes of therapy discontinuity in the male subjects.

Research frontiers

The aim of this study was to demonstrate the efficacy, safety and tolerability of a prompt pharmacologic treatment with the combination valsartan plus hydrochlorothiazide in young-middle aged male subjects with slight hypertension and presence of target organ damage.

Innovations and breakthroughs

The results of this study show that an early pharmacologic treatment with the combination valsartan plus hydrochlorothiazide (160 and 25 mg daily, respectively) in 20 young or middle-aged men with high-normal BP or first degree hypertension with evidence of target organ damage, is very effective and well tolerated. Indeed, already after 3 mo of treatment, BP was significantly reduced both at rest and during exercise, the proportion of patients reaching BP normalization (BP < 130/85 mmHg) being very high (85%). Similarly, the treatment was very effective in counteracting target organ damage, thus highly reducing the cardiovascular risk. In particular, left ventricular mass and relative wall thickness were significantly reduced; concentric left ventricular hypertrophy was present in 70% of subjects at the study entry and only in 5% after 3 mo of treatment. In addition, the antihypertensive therapy used did not affect the erectile function in our patients, with good compliance to treatment.

Applications

A prompt pharmacologic treatment should be applied in subjects with high-normal BP, first degree hypertension with evidence of target organ damage, in order to normalize BP and revert vascular and cardiac remodeling. The combination valsartan plus hydrochlorothiazide could be a good choice.

Peer review

The paper is well written and the conclusions are clear. Only a limited number of subjects were studied but they served as their own controls. References are appropriate.

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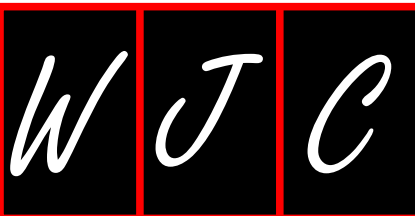
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Meetings

Events Calendar 2010

January 12-13
Riyadh, Saudi Arabia
1st International Cardiovascular
Pharmacotherapy Conference

January 17-21
Hollywood, United States
22nd Annual International
Symposium on Endovascular Therapy

January 20-23
Sao Paulo, Brazil
World Cardiology, Metabolism and
Thrombosis Congress

January 21-24
Phoenix, United States
13th Society for Cardiovascular
Magnetic Resonance Annual
Scientific Sessions

January 28-30
Brussels, Belgium
29th Belgian Society of Cardiology
Annual Scientific Meeting

January 28-31
Nashville, United States
31st Annual Meeting of
The American Academy of
Cardiovascular Perfusion

February 3-6
Snowbird, United States
35th Annual Cardiovascular
Conference at Snowbird

February 4-5
Leuven, Belgium
Leuven Symposium on Myocardial
Velocity and Deformation Imaging

February 6-9
St. Petersburg, United States
10th Annual International
Symposium on Congenital Heart
Disease

February 8-10
Tel Aviv, Israel
10th International Dead Sea
Symposium on Cardiac Arrhythmias
and Device Therapy

February 11-12
London, United Kingdom
2nd National Chronic Heart Failure
and Hypertension

February 18-21
Istanbul, Turkey
The 2nd World Congress on
Controversies in Cardiovascular
Disease (C-Care)

February 22-25
Maui, United States
Arrhythmias & the Heart
Symposium

February 22-26
Cancun, Mexico
15th Annual Cardiology at Cancun-
Advances in Clinical Cardiology and
Multi-Modality Imaging

February 25-28
Valencia, Spain
First International Meeting on
Cardiac Problems in Pregnancy

February 26-28
Hong Kong, China
International Congress of
Cardiology

February 28-March 4
Scottsdale, United States
International Congress XXIII on
Endovascular Interventions

February 28-March 5
Keystone, United States
Keystone Symposia: Cardiovascular
Development and Repair (X2)

March 3-5
Kish Island, Iran
Islamic Republic of 4th Middle East
Cardiovascular Congress

March 4-7
Newport Beach, United States
30th Annual CREF: Cardiothoracic
Surgery Symposium

March 7-12
Snowmass Village, United States
Interventional Cardiology 2010: 25th
Annual International Symposium

March 14-16
Atlanta, United States
American College of Cardiology
59th Annual Scientific Session

March 18-20
Rome, Italy
VIII Congress of the Italian Society
of Cardiovascular Prevention

March 18-20
Prague, Czech Republic
XI International Forum for the
Evaluation of Cardiovascular Care

March 24-25
Jeddah, Saudi Arabia
12th KFAFH Cardiovascular
Conference: A balanced approach to
treatment of cardiovascular diseases

April 8-11
Guangzhou, China
The 12th South China International
Congress of Cardiology

April 14-15
Tel Aviv, Israel
The 57th Annual Congress of the
Israel Heart Society in Association
with The Israel Society of
Cardiothoracic Surgery

April 15-18
Izmir, Turkey
59th European Society for
Cardiovascular Surgery
International Congress

May 5-7
Prague, Czech Republic
EuroPrevent 2010-Cardiovascular
Prevention: a Lifelong Challenge

May 8-9
St. Paul, United States
Controversies in Cardiovascular
Disease: Practical Approaches to
Complex Problems: Medical and
Surgical

May 12-16
Marrakesh, Morocco
7th Metabolic Syndrome, type
II Diabetes and Atherosclerosis
Congress

May 17-20
Whistler, Canada
6th IAS-Sponsored HDL Workshop
on High Density Lipoproteins

May 21-22
Sydney, Australia
3rd Cardiovascular CT, Concord
Conference 2010

May 29-June 1
Berlin, Germany
Heart Failure Congress 2010

June 1-4
Seoul, Korea, Republic of
9th Asian-Pacific Congress of
Cardiovascular & Interventional
Radiology (APCCVIR 2010)

June 16-19
Beijing, China
World Congress of Cardiology
Scientific Sessions

June 17-19
Port El Kantaoui, Tunisia
The 7th Tunisian and Europeans
Days of Cardiology Practice

July 1-3
Singapore, Singapore
6th Asian Interventional
Cardiovascular Therapeutics
Congress

July 16-19
Berlin, Germany
Frontiers in CardioVascular Biology
2010-1st Meeting of the CBCS of the
ESC

July 24-27
Vancouver, Canada
15th World Congress on Heart
Disease, Annual Scientific Sessions
2010

August 13-15
Krabi, Thailand
East Meets West Cardiology 2010

September 16-18
Athens, Greece
5th International Meeting of the
Onassis Cardiac Surgery Center

September 25-29
Belo Horizonte, Brazil
65th Brazilian Congress of
Cardiology

September 30-October 2
Berlin, Germany
5th International Symposium
on Integrated Biomarkers in
Cardiovascular Diseases

October 10-13
Rochester, United States
26th Annual Echocardiography
in Pediatric and Adult Congenital
Heart Disease Symposium

October 16-19
Copenhagen, Denmark
Acute Cardiac Care 2010

October 20-23
Boston, United States
2010 Cardiometabolic Health
Congress

November 25-26
London, United Kingdom
13th British Society for Heart Failure
Annual Meeting

December 9-11
Lisbon, Portugal
Heart, Vessels & Diabetes-The
European Conference

Instructions to authors

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- 5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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Patent (list all authors)

- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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Write as mean \pm SD or mean \pm SE.

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