Skeletal Muscle Ventricles for Cardiac Assistance

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Abstract:
Autologous skeletal muscle can be used for cardiac assistance if the problem of muscle fatigue is overcome with electrical conditioning administered via its motor nerve.
Skeletal muscle ventricles (SMVs) have been constructed using latissimus dorsi muscle, after several weeks of vascular delay and electrical conditioning SMVs can be connected to the circulation where they can be electrically stimulated to contract to assist the heart. SMVs of different design have been developed and used in dogs for left ventricular assistance as aortic diastolic counterpulsators and for right ventricular assistance in a modified Rastelli configuration, long-term survival has been achieved. One dog has remained in good condition with an SMV performing useful work in circulation for more than two years.
Although still experimental SMVs are a promising alternative for the future treatment of patients with terminal cardiac failure.
Key words: Skeletal muscle ventricles, muscle fatigue, muscle conditioning, vascular delay.

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End-stage heart failure of various etiologies represents not only a cause of significant morbidity and mortality for the affected patients but also a challenge to the clinicians charged with their care. Currently these terminally ill patients have a very limited life expectancy. The progress and results achieved by cardiac transplantation are well recognized, but the shortage of organ donations remains a significant problem, so that many patients die while waiting for a suitable donor. In an effort to find therapeutic alternatives for end-stage heart failure several investigators have studied the possible use of skeletal muscle for cardiac assistance. What makes the use of autologous skeletal muscle attractive is its availability, its potential for growth if used in young subjects, the absence of rejection, and, last but not least in the current health-care economic situation, a potentially favorable cost-benefit relationship.

Early Contributions

The extensive experimental studies dealing with skeletal muscle cardiac assist over the past twelve years were preceded by earlier attempts, which were, however, disadvantaged by the limited existing state of knowledge of the relevant basic muscle physiology [22,23,24,25,45,46].

Kantrowitz and his colleagues [23] were the first to attempt cardiac assistance using skeletal muscle by suturing a pedicle of diaphragm directly to the heart. When the skeletal muscle flap was stimulated to contract during systole no hemodynamic effect was detected. They then wrapped a pedicle of diaphragm around the descending thoracic aorta and stimulated it to contract during diastole as a counterpulsator. This time significant diastolic augmentation was recorded for 15 seconds, at which point muscle fatigue developed [23,24]. Other experiments had similar results, major advances could not occur until the problem of muscle fatigue had been solved. Progress toward the solution came from the contribution of two groups of basic scientists.

In the early 1960's, Buller, Eccles and Eccles [16] performed experiments involving cross-anastomosis of the motor nerves supplying skeletal muscles of different type. These experiments showed that the physiological properties of adult mammalian skeletal muscles were under neural influence [15,16]. A few years later Salmons and Vrbova [44] showed that similar changes in physiological properties could be evoked by low-frequency electrical stimulation of the motor nerve. By using a combination of cross-innervation and stimulation, Salmons and Sreter [43] established that the

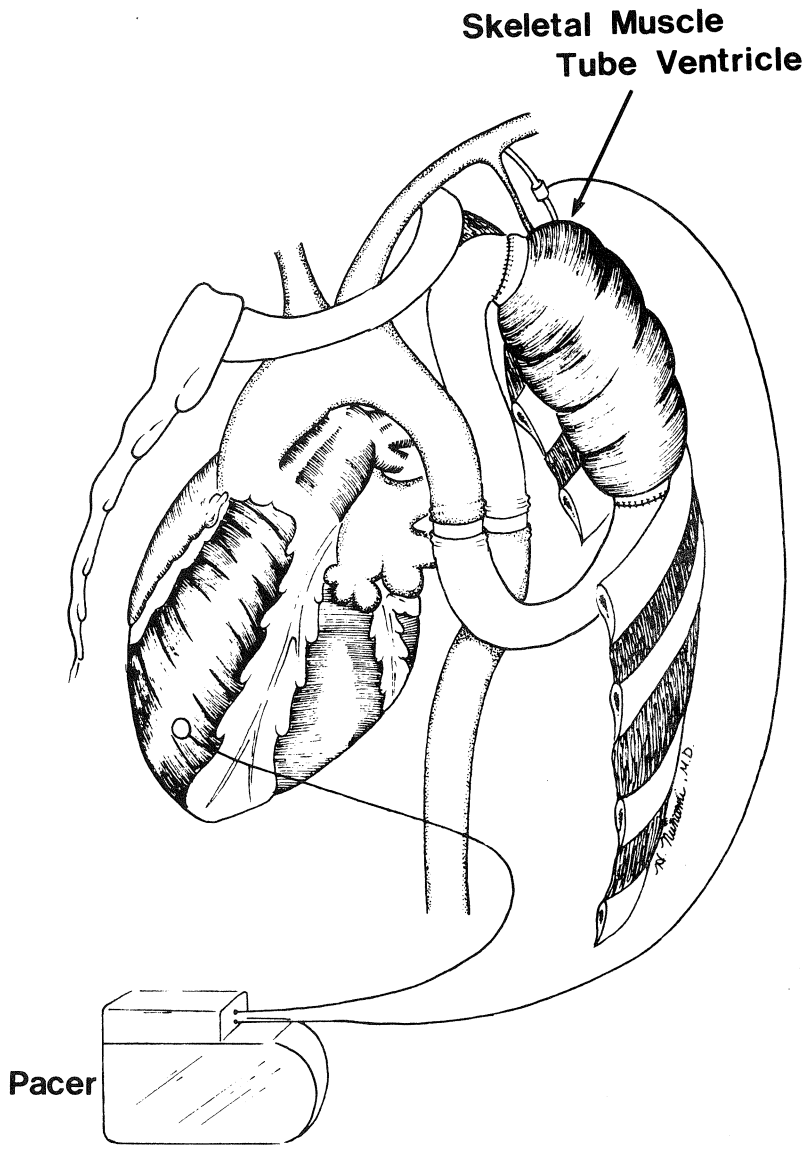

Figure 1: Cylindrical skeletal muscle ventricle in circulation, inflow at one end, outflow at the other.

pattern of impulse activity imposed on a muscle by its motor nerve was responsible for determining its type, a muscle populated predominantly by fast-twitch fatigue-prone fibers could be transformed into one rich in slow-twitch fatigue-resistant fibers [42]. It seemed that it might be possible to exploit this phenomenon of muscle transformation for skeletal muscle cardiac assistance [10,20,27].

These developments created renewed interest in the use of skeletal muscle for cardiac assistance. One approach has since achieved clinical implementation. This consists of wrapping a muscle around the heart or replacing a portion of the cardiac wall with skeletal muscle; the muscle is then stimulated by a progressive protocol to contract in synchrony with the heart. Following initial clinical reports from Carpentier in France and Magovern in the United States this procedure became known as cardiomyoplasty [17,33]. A limited but important clinical experience with this technique has now accumulated, with more than 100 patients undergoing cardiomyoplasty around the world. It appears that cardiomyoplasty usually provides subjective symptomatic improvement in patients with cardiac failure and in some cases there is also objective evidence of hemodynamic improvement [18,21,32].

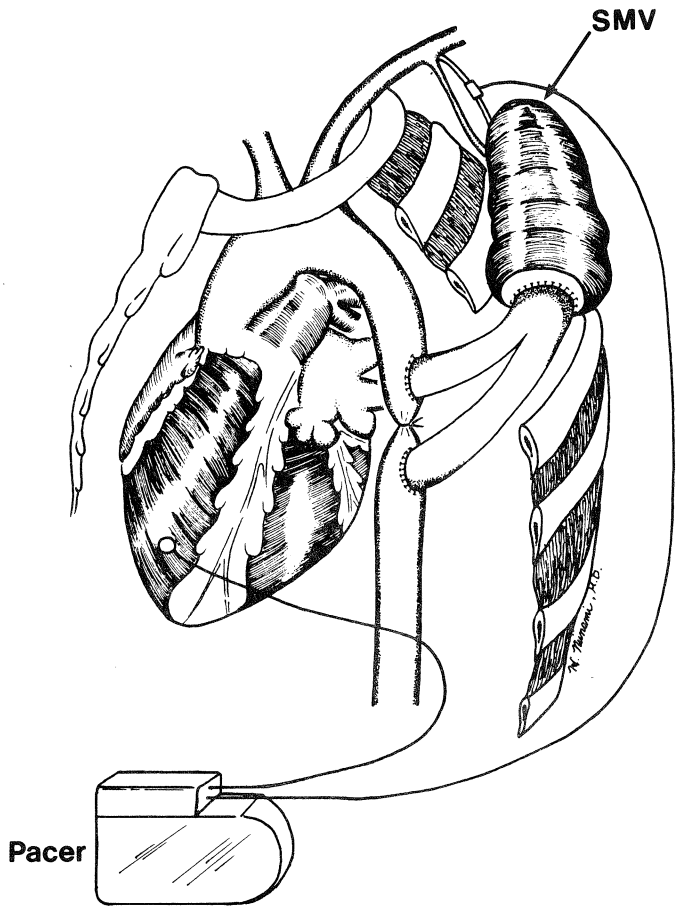

Figure 2: Skeletal muscle ventricle (SMV) in circulation. Note the bifurcated PTFE graft and the ligation of the aorta between the two limbs of the graft.

In the laboratories at University of Pennsylvania and subsequently at Wayne State University, the research has pursued a different goal: the development of pumping chambers constructed from skeletal muscle that are capable of pumping blood in the circulation in a manner similar to the native ventricles, providing cardiac assistance. These pumping chambers are referred to as skeletal muscle ventricles (SMVs). The purpose of this review is to describe the progress that has been achieved to date with this approach.

Skeletal Muscle Ventricle Construction

SMVs have been constructed from several skeletal muscles including diaphragm, rectus abdominis, quadriceps femoris, gluteus maximus [22,25,45,46], but the most extensive experience and best results have been obtained with the latissimus dorsi muscle. The latissimus dorsi muscle has several features that make it ideal for SMVs: it is a large, broad-based, paired muscle of the back that can be mobilized surgically without difficulty; its mass is comparable to the mass of the left ventricle; it is reasonably close to the heart and the major vessels. Its original function is not critical and transfer does not cause significant physical impairment. Finally, and of great importance, this muscle is supplied by one main neurovascular bundle that can be readily identified and protected, and is accessible for electrical stimulation of the motor nerve.

The technique of construction of an SMV using latissimus dorsi muscle is well established. Either the left or the right muscle can be used depending on the planned type of connection to the circulation. At a first operation (Phase I), the latissimus dorsi muscle is dissected from the subcutaneous tissue and the chest wall. Insertions on the spine, the lower ribs and the iliac crest are divided but the insertion on the humerus is preserved. The thoracodorsal nerve, artery and vein are then identified on the deep surface of the muscle as proximally as possible, and a nerve electrode is either passed

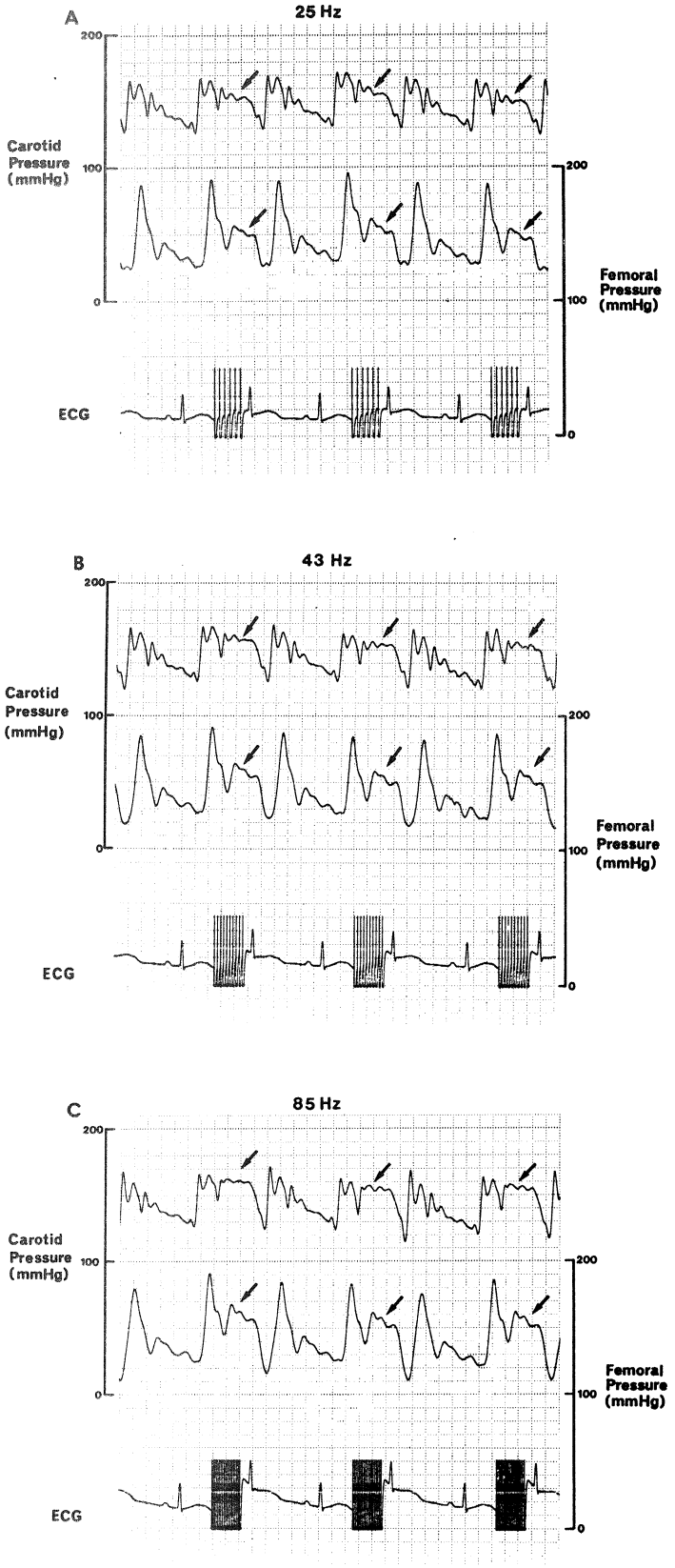

Figure 3: Skeletal muscle ventricle in circulation, 24-month follow-up: carotid pressure, femoral pressure and ECG tracings at 25, 43 and 85 Hz burst stimulation frequencies (Figure 3a, 3b and 3c respectively). Arrows mark diastolic augmentation. Note the burst stimulation artifact superimposed on the ECG.

around the main trunk of the nerve or fixed close to it with sutures.

The skeletal muscle ventricle is then constructed by wrapping the latissimus dorsi muscle around a mandrel. The mandrel varies in shape and volume according to the desired SMV configuration. Fixation of the muscle wrap to the mandrel is obtained using a Dacron sewing ring. The nerve electrode is connected with a lead to a pacemaker-like neurostimulator (Itrel, Medtronic, Inc., Minneapolis, MN) that is usually placed in a pocket under the rectus abdominis muscle. At the conclusion of this first operation the SMV has usually been left in the subcutaneous tissue, more recently it has been placed inside the chest through a small posterior thoracotomy.

The second operation (Phase II), is performed several weeks later. A thoracotomy or a median sternotomy is performed and the SMV is connected to the circulation. At this time the pericardium is incised and a sensing lead is secured to the left ventricular epicardium. The neurostimulator is removed and replaced with a specially designed programmable Cardiomyostimulator^{TM} (Medtronic, Inc., Minneapolis, MN). After being connected to both the thoracodorsal nerve electrode and the epicardial lead the Cardiomyostimulator^{TM} is capable of sensing the cardiac electrical activity and initiating contraction of the SMV after an appropriate delay. SMVs have been connected to the circulation in various ways, which will be discussed below. At this point it is necessary to stress the importance of the delay interval between the Phase I and the Phase II operations. During this time the layers of the muscle wrap become adherent to each other, temporary muscle ischemia resolves, and electrical conditioning can be accomplished.

Progress in SMV Development

In the early 1980's Macoviak studied the application of electrical conditioning to skeletal muscle and used paced muscle grafts of diaphragm to replace ventricular myocardium [26-30]. Both Macoviak and Armenti were able to show that resistance to fatigue developed not only with continuous stimulation at 10Hz, as done by Salmons and Vrbova, but also with continuous stimulation at 2 Hz at intervals similar to the natural heart rate [10,27].

The mechanisms underlying fatigue resistance have been studied by measurements of oxygen consumption in conditioned skeletal muscle challenged with a fatiguing pattern of stimulation. Metabolite levels have also been measured by ^{31}P nuclear magnetic resonance. These studies demonstrated changes in histochemical and enzymatic profile associated with the development of fatigue resistance [2,11,12,14,19,35].

A finding that emerged early in the experiments with SMVs was the importance of a period of rest, or vascular delay, between constructing the SMV and then activating it to do work. This delay period is necessary for the latissimus muscle to recover from the temporary ischemia that follows the surgical dissection, when small subcutaneous and chest wall arteries that supply the distal portion of the muscle are divided [37-39].

Mannion evaluated the performance of SMVs with and without vascular delay and electrical conditioning. The skeletal muscle ventricles were connected to an external mock circulation device. Those that had undergone both vascular delay and conditioning pumped effectively for several hours with only a small decline in function, while SMVs not allowed to recover from ischemia and not conditioned fatigued in a few minutes [37]. Later on it was shown that after the vascular delay SMVs constructed in dogs could undergo conditioning while performing useful work [1,4].

In a subsequent experiment Mannion connected skeletal muscle ventricles to the descending aorta using a valved T-tube circuit. With the SMVs stimulated to contract in diastole as counterpulsators, good function was recorded for a maximum of 14 hours, SMVs stroke work at levels intermediate between those of the canine right and left cardiac ventricles were obtained [34,36].

In an attempt to determine whether SMVs could perform at these levels for prolonged periods a totally implantable mock circulation device was developed. When SMVs were connected to the mock circulation device with preload and afterload set at 30 and 80 mmHg respectively, pumping was maintained for up to 9 weeks [3,4].

Acker then constructed SMVs in a cylindrical configuration, with inflow at one end and outflow at the other, so that the aortic blood flow passed from end to end through the SMV (Figure 1). After a period of vascular delay these SMVs were connected to the descending aorta and were operated as aortic diastolic counterpulsators. With this design long-term survival in circulation was achieved for the first time. One dog survived for 7 weeks and another for 11 weeks with their SMVs pumping blood effectively [1]. The eventual cause of death in these two animals was renal failure due to distal embolization originating from thrombus forming inside the SMV.

Other devices were also tested [8]. In one experiment the SMV compressed a bladder filled with gas or fluid that in turn compressed a polyurethane-lined pump which functioned as a diastolic aortic counterpulsator. This device worked well in one animal for 42 days until the aorta ruptured [9].

In 1989 Anderson developed an improved SMV for cardiac assist. The latissimus dorsi muscle was wrapped around a conical Teflon mandrel, and after 4 weeks of vascular delay a bifurcated PTFE graft was used for connection to the descending thoracic aorta (Figure 2). To address the problem of thromboembolization the inner cavity of these SMVs was lined with autologous pleura or pericardium. To ensure obligatory blood flow through the SMV the aorta was ligated between the two limbs of the synthetic graft. An R-wave synchronized burst pulse generator (SP 1005, Medtronic, Inc., Minneapolis, MN) was then used to stimulate the SMV during diastole as a counterpulsator. Significant diastolic augmentation was recorded and maintained for prolonged periods [5,6]. To date one dog from that study is alive and well 24 months after surgery, with continued effective diastolic augmentation (Figure 3) [41]. To the best of our knowledge, this is the longest reported survival of any laboratory animal with an SMV or any other type of mechanical assist device in circulation.

SMVs have been used in circulation mostly as diastolic counterpulsators because it was originally thought that high preloads would be needed for optimal performance. With better understanding of muscle mechanics and compliance, SMVs have recently been shown to function well at low preloads, suggesting that they can be used for right heart assistance. Following earlier attempts by Macoviak [31], Bridges connected an SMV to both venae cavae and to the

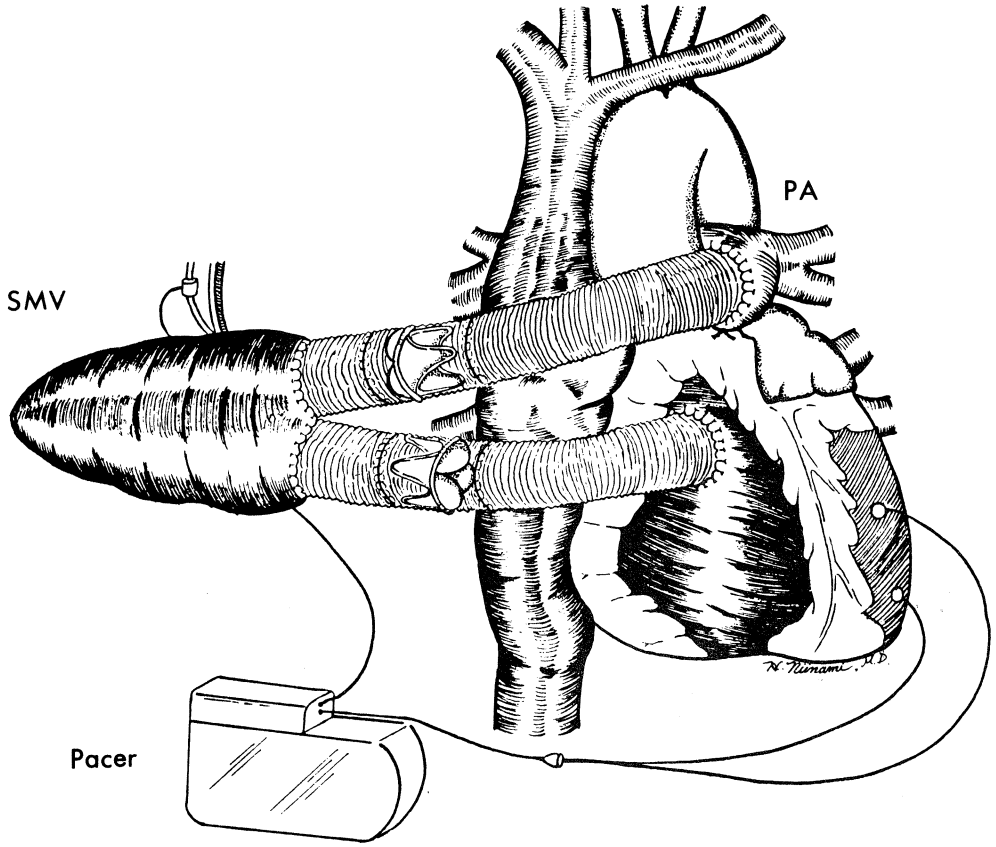

Figure 4: Skeletal muscle ventricle (SMV) in circulation for right heart assistance, Rastelli configuration. Note that the pulmonary artery is ligated at its origin.

pulmonary artery using synthetic valved conduits, thus diverting systemic venous return through the SMV. Right heart bypass was achieved at near physiological preloads for several hours [13]. More recently, chronic survival was obtained with SMVs in series with the heart, using a modified Rastelli configuration that conducts blood from the right ventricle through a valved conduit to an SMV and then through a second valved conduit to the main pulmonary artery. In this model the pulmonary artery is ligated proximal to the anastomosis with the second valved conduit (Figure 4) [40].

Currently the group at Wayne State University is testing SMVs that are smaller and thicker-walled than in previous designs. They perform well at low preloads and have been able to generate adequate power and flow when connected with two aortic valved homografts to the left atrium and to the descending aorta to function as left ventricular assist devices.

In the past SMVs have been constructed and left outside the chest in the subcutaneous tissue. Recently they have been placed inside the chest at the apex of the pleural cavity. The SMVs are better protected in that location and appear to perform better from a mechanical point of view. Respiratory problems related to the intrathoracic position have not been encountered so far (unpublished data).

Conclusions

SMVs remain an experimental form of cardiac assist and further work will be required before they can be used clinically. Areas that require attention are the prevention of thromboembolism, the evaluation of alternative electrical conditioning protocols and the development of a reliable animal model of cardiac failure. We are, however, encouraged by the results achieved to date. We believe that with better understanding of muscle conditioning, improvement in SMV design and identification of the optimal connection to

the circulation, SMVs are likely to provide a valuable palliative treatment for patients with end-stage heart failure.

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