Developing New Treatment Strategies for Heart Failure: A Challenge in the New Millennium

Different Models of Heart Failure as a Guide to Therapy

“Heart failure is the state of any heart disease in which . . . the heart is unable to pump blood at a rate adequate for satisfying the requirements of the tissues.”¹ This basic definition of heart failure represents the fundamental approach to the clinical syndrome of cardiac failure and many treatment strategies are aimed at enhancing myocardial contractility and increasing cardiac index. However, in the light of recent investigations, this definition may not be sufficient to explain some relevant characteristics of “heart failure.” Whereas the traditional cardiorenal or cardiocirculatory model of congestive cardiac failure emphasized salt and water retention in combination with the altered cardiac pumping capacity, the insidious disease progression accompanied by left ventricular dilation and alterations in left ventricular geometry are now regarded as crucial steps in the development of heart failure. These observations gave rise to a novel, so-called “progressive” model of heart failure,² in which several biochemical molecules, such as hormone-like substances and chemokines, have been put forward as potential mediators of left ventricular remodeling, in effect leading to deterioration in ventricular function and symptoms over time.³ Moreover, in the last decades, convincing investigations demonstrated beneficial effects of treatment strategies, derived from this “progressive” or “neurohormonal” model, such as angiotensin-converting enzyme inhibition,⁴,⁵ angiotensin II receptor inhibition,⁶ β-adrenoceptor-blocking interventions,⁷ and aldosterone antagonism.⁸,⁹ A significant benefit with respect to mortality, morbidity, and also quality of life could be achieved in large-scale trials using these pharmacologic classes or a combination of them. Therefore, any novel therapy targeting symptoms and prognosis of heart failure, including the novel techniques of cellular cardiomyoplasty, will be compared with and/or added to the current state of medical (and also interventional) treatment.

Cell Therapy: Inspired by the Cardiocirculatory Model of Heart Failure

As a new potential treatment strategy, transplantation of cells with the potential of forming contractile elements has been extensively evaluated in experimental investigations. The principal idea was to replace scar tissue after myocardial infarction by transplanting immature cardiomyocytes, skeletal myoblasts, or stem cells of various origin (embryonic or mesenchymal), which should proliferate and thereafter form contractile tissue (Figure 5.1). Therefore, the main principles of cardiac cell

Cell Therapy for Heart Failure
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transplantation are derived from a cardiocirculatory model of heart failure, emphasizing the altered pumping capacity of the heart as the main therapeutic target of the disease. The initial goal of cell therapy was to completely rebuild the infarcted part of the heart by actively and synchronously contracting myocardium-like tissue, finally restoring cardiac pumping capacity. As discussed in the following paragraphs, this goal has not yet completely been accomplished: In recent years, several studies demonstrated the feasibility of various techniques of transplanting cells of different origin and state of differentiation. Some specific techniques and cell types have already been tested in clinical trials. Moreover, in a wide range of basic science models, important prerequisites for successful cell engraftment could be demonstrated: Survival of the transplant with the formation of a viable graft within the myocardial tissue was obvious in various experimental studies with observational periods for up to 6–12 months after transplantation. Vascularization of the graft tissue with effective regional blood flow appears to develop under certain conditions, and also some degree of differentiation of immature cell types seems to be achievable in different experimental settings, which could be demonstrated as morphologic signs at histologic examination and on the basis of the expression of biochemical markers. Important issues requiring further investigations in this field are related to the improvement of integration of grafted tissue into its host, which on the one hand means the spatial distribution of the grafted cells within the host and on the other hand meaning the development of effective cell-to-cell contacts, unifying both parts—the host and the graft. Nonetheless, after all these basics of experimental research, some pivotal questions, regarding not only the effects on regional and global contractile function, but also the influence on disease progression and remodeling need to be answered (Figure 5.1): Does the transplanted tissue contribute to contractile...
myocardial performance? How does transplantation affect ventricular geometry and hemodynamics over time? Can progression of heart failure be attenuated? Does the procedure relieve symptoms of heart failure, and is survival in transplanted individuals significantly different from nontransplanted controls?

Some Basics

Different Cell Types

The main sources of cells for transplantation that have been studied in models of myocardial damage are firstly immature cardiomyocytes (i.e., embryonic or fetal cardiac cells, harvested in utero at a specified gestational age) that conserve a certain potential of proliferation, secondly skeletal myoblasts, harvested from fully differentiated skeletal muscles, the so-called satellite cells, and thirdly stem cells, either derived from the bone marrow or as embryonic stem cells. These various sources for myocardial regeneration are characterized by numerous differences with respect to stage of differentiation, proliferative capacity, plasticity of phenotype, etc. However, a prerequisite for these cells to generate a graft, which actively contributes to contractile force, is at least in theory, a certain degree of differentiation into a “contractile phenotype.” The following discussion of the potential of these cells for treatment of heart failure will therefore focus on transplantation of immature cardiomyocytes, which in our opinion can be regarded as the basic scientific model of what can be achieved by cell therapy. In practice, the greater availability of cells from other sources and for some cell types also their autologous character without need for immunosuppression may be the most important arguments for using other cells than cardiomyocytes for cellular cardiomyoplasty when reaching the level of clinical application.

Survival and Proliferation After Transplantation

In most experimental cell grafting studies, a suspension of the cells was injected into the myocardium or the infarcted/cryoinjured part of the left ventricle via an epicardial approach. Pilot studies had shown that, for example, injection of fetal or neonatal cardiomyocytes into a rat hindlimb resulted in a spontaneously contracting tissue that increased in size over the first 2 weeks and developed sarcomeres. The feasibility of direct intramyocardial injection of cultured fetal cardiomyocytes into normal mice hearts, was first demonstrated by Soonpaa et al. The grafted cells survived more than 8 weeks, and formed intercalated disks, as shown by electron microscopy. In the rat, the injected suspension of immature cardiomyocytes formed a “pocket” of packed cells within the myocardium right after transplantation. Thereafter, they tended to form clusters of cells with increasingly organized pattern and signs of differentiation. Using a quantitative analysis (based on the detection of the Sry gene on the Y chromosome after transplantation of male cells into female recipients), Müller-Ehmsen et al. reported a survival rate of 15% 12 weeks after transplantation of neonatal cardiomyocytes into normal myocardium. In contrast, 6 months after transplantation of neonatal cardiomyocytes into infarcted myocardium (permanent coronary artery ligation), approximately 60% of the initially injected number of cells was still detectable. One might speculate that transplanted cells in normal myocardium are more likely to be lost through the intact vasculature, whereas cells injected into an ischemic zone are more likely to stay in place.

The success of engraftment depends on the type of injected cells and also on the time between myocardial injury and transplantation. As shown by Reinecke et al., cultured fetal and neonatal cardiomyocyte suspensions transplanted into normal hearts, acutely cryoinjured hearts, and 6-day-old cryoinjured hearts (“granulation tissue”) survived up to 8 weeks after transplantation, whereas transplanted adult cardiomyocytes showed evidence of coagulation necrosis already by 1 day after transplantation. Better survival of the graft was also demonstrated when transplantation was performed 2 weeks after cryoinjury (granulation tissue) in comparison with transplantation early after myocardial injury, when the acute inflammatory response after myocardial necrosis had calmed down.

However, the degree of proliferation after transplantation might also determine the final size of the graft and its spatial distribution and integration within the host tissue. Only cardiomyocytes in the stage of hyperplastic growth,
such as fetal and neonatal cardiomyocytes (in contrast to adult cardiomyocytes), survive after transplantation. In the investigations by Reinecke et al., neonatal cardiomyocytes were positive for PCNA (proliferating cell nuclear antigen) only during the first 2 weeks after transplantation with a peak at day 6. Labeling with tritiated thymidine in mice cardiomyocytes (as an indicator for DNA synthesis) demonstrated 29% positive embryonic donor cardiomyocytes before transplantation (gestational day 15), but 19 days after transplantation only 0.6% of the surviving cells showed evidence of DNA synthesis. Thus, proliferative growth of the transplanted cells might significantly contribute to colonization of the host, but it decreases substantially within the first weeks after transplantation.

Although the mentioned investigations on survival and proliferation mainly apply to fetal and neonatal cardiomyocytes, the same aspects are to be considered for other cell types as well, and enhancing survival or proliferation could improve the outcome. For optimizing the success of transplantation, several techniques, such as stimulation of proliferation by altered expression of selected genes (e.g., overexpression of fibroblast growth factor-2 isoforms, overexpression of cyclin D1), modifying the culturing technique, or new methods of tissue processing before transplantation, have been suggested. For example, pretreatment of skeletal muscles before harvesting skeletal myoblasts (e.g., preinjecting of bupivacaine as a pharmacologic stressor to activate satellite cells) was proposed by Pouzet et al. for improving skeletal myoblast transplantation. Heat shock treatment or anti-apoptosis interventions were also tested to reduce posttransplantation death. Culturing the cells in three-dimensional scaffolds of various materials, so-called tissue engineering, seems to be a promising approach to overcome some of the current problems of limited survival, engraftment, and integration.

**Differentiation and Integration**

Depending on the type of cell used for transplantation, development of the “contractile phenotype” requires a certain period of differentiation. Although methods and obstacles of inducing differentiation in stem cells will be discussed in other chapters of this book, immature cardiomyocytes also require a significant period of time to develop morphologic signs of differentiation (increase in diameter, decrease of nucleus-to-cytoplasm ratio, the development of sarcomeric striation, etc.) and biochemical and ultrastructural markers of differentiation (myofibrils, desmosomes, connexin 43, etc.). A short look at Figure 5.2 (see color section), comparing normal myocardium (left) and graft tissue, 4 weeks after transplantation of neonatal cardiomyocytes into a permanent occlusion infarct (right), illustrates incomplete differentiation and integration at first sight. There is substantial disarray in the overall orientation of the cells within the graft and sarcomeric striations are less organized in comparison with normal myocardium.

The temporal development of differentiation after transplantation of immature myocytes in the experiments by Reinecke et al. was characterized by a progressive increase in graft-cell diameter up to 8 weeks posttransplantation, without reaching the range of host myocyte diameters. These results indicate a switch from hyperplastic to hypertrophic growth, which parallels the observations on graft proliferative activity. Li et al. compared cultured fetal cardiomyocytes with cardiomyocytes 4 weeks after transplantation into cryoinjured heart by light and electron microscopy. Initially, the cells were spherical and the myofilaments were disorganized without sarcomeres, but, after 4 weeks, the grafts contained sarcomeres and cellular junctions composed of desmosomes and fascia adherens. Electron microscopy studies in the transplant experiments (into normal hosts) by Soonpaa et al. demonstrated a high degree of differentiation with myofibrillae forming complete sarcomeres, numerous junctional complexes between cells, and abundant mitochondria, which obviously did not allow distinguishing them from host cardiomyocytes. However, various studies reported that transplanted fetal tissue was positive for α-actin (fetal heart isoform) up to 65 days after transplantation. Therefore, differentiation remains incomplete with respect to morphologic and biochemical markers.

Integration into the host is another unresolved issue. For cardiac systolic function with synchronous contractions of the myocardium, it is crucial to form a mechanical and electrical syncytium. Whereas transplanting immature cardiomyocytes into a normal (noninfarcted) myocardium seems to result in relatively effective host-to-graft coupling with the formation of
intercalated disks between the myocytes,\textsuperscript{23} the results in injured hearts with scar formation are less promising.

In the aforementioned study by Reinecke et al.,\textsuperscript{25} neonatal cardiomyocytes expressed the adherens junction protein N-cadherin and connexin 43, initially circumferential and thereafter restricted to intercalated disks. Host and graft cells showed a close spatial approximation early after transplantation, but by 2 and 8 weeks, most grafts were separated from the host by granulation or scar tissue. Contact sites between host and graft were demonstrated in 40% of the hearts only at the peripheral sites of the graft. Using confocal microscopy, in some (rare) cases gap junctions between host and graft were detectable. Connold et al.\textsuperscript{36} reported similar results with respect to the development of cell-to-cell coupling in a study transplanting fetal cardiomyocytes with a follow-up period of up to 7 months. In a short-term follow-up after fetal cardiomyocyte transplantation, connexin 43, desmoplakin, and cadherin were demonstrated to be localized between grafted cardiomyocytes, which tended to align parallel to host cardiomyocytes, and between grafted and host cardiomyocytes.\textsuperscript{37} Thus, coupling between grafted and host cells occurs, but within a scar, separation of the graft from remote tissue, in particular later after transplantation, might hinder effective integration of the graft.

At 6 months after transplantation, Müller-Ehmsen et al.\textsuperscript{15} described the graft as “large confluent clusters of myocardial cells in the scar.” Figure 5.3 (see color section) shows an example from our laboratory showing the graft 4 weeks after transplantation of neonatal cardiomyocytes into the infarcted tissue, produced by permanent coronary artery occlusion in the rat. A significant separation of the graft from host tissue develops by the disposition of collagen and connective tissue [Figure 5.3 (see color section)].

Despite positive immunostaining for connexin 43 at junctions between grafted cells in the study by Müller-Ehmsen et al., no gap junctions between host and graft were demonstrated in this 6 months follow-up.\textsuperscript{15} Although Connold et al.\textsuperscript{36} suggested a certain degree of migration of the transplanted cells over the surface of the left ventricle after 5–7 months, the majority of the graft was found at the site of the injection. In summary, the integration of grafted cells appears to remain incomplete, mainly because of separation by scar tissue with longer periods of follow-up, despite the principal possibility of cell-to-cell connections between host and graft.

**Vascularization of the Graft**

In early transplant studies, when fetal cardiac tissue was transplanted into a nonphysiological environment, such as the anterior eye chamber,\textsuperscript{38} it was remarkable that the development and growth of the hearts in these investigations was always accompanied by vascularization of the tissue. In long-term studies on transplantation of embryonic cardiomyocytes into the heart, an increased vascularization of the graft was shown up to 53 days.\textsuperscript{35} Another transplant investigation demonstrated a markedly increased capillary density along with a non-significant improvement of regional myocardial blood flow after cardiomyocyte grafting into 3-week-old scars, created by cryoinjury. Transfection of the donor cells with a plasmid encoding vascular endothelial growth factor further enhanced angiogenesis in this study.\textsuperscript{39} Recently, we measured regional myocardial blood flow by radioactive microspheres and capillary density in a permanent coronary artery occlusion model with transplantation of neonatal cardiomyocytes. Four weeks after transplantation, a significantly higher regional blood flow in the infarcted tissue was demonstrated in the transplant group (see Table 5.1), showing that neovascularization in response to cell therapy results in effective enhancement of tissue perfusion. Counting of perfused capillaries in the scar clearly demonstrated that neovascularization was confined to regions of successful engraftment, whereas scar tissue in the transplant and medium group contained the same number of capillaries.\textsuperscript{18} Therefore, the grafted cells seem to induce a vasculature to nourish them, which effectively increases directed regional flow.

**Effects on Left Ventricular Performance**

Although, as discussed above, important prerequisites for success of cell therapy have been demonstrated, the central question of how and
to what extent the graft contributes to cardiac contractile force is much more difficult to answer. Looking at the marked disarray in the organization of the graft in Figure 5.2 (see color section) or the huge amount of connective tissue separating the host and the graft in Figure 5.3 (see color section), it is difficult to conceive how these grafts could effectively contribute to synchronous contractions of the heart.40

However, it is likely that the graft created by the described techniques of transplantation has the principal capacity of contracting.41 When the tissue formed 4 weeks after transplantation of fetal cardiomyocytes into cryoinjured hearts was excised, it “appeared to beat spontaneously and regularly at the time of explantation.”42 Because the function depends crucially on synchronous contractions of the cells, it is important to mention a recent study, which was the first to show synchronized and organized propagation of calcium-transients from host to graft cells in mice experiments of transplanting cardiomyocytes in noninjured myocardium.43 Although not absolutely proving synchronous contractions of the host and the graft, this is, nonetheless, a very strong argument in favor of the efficacy of host and graft coupling via intercalated disks. However, these studies were performed in noninjured hearts, where host and graft might be much more juxtaposed than in scarred parts of the left ventricle.

After transplantation of cells into scar tissue or infarcted myocardium, the integration into the host, especially in studies with longer follow-up, remains incomplete. Already Reinecke et al.25 reported the tendency of separation by collagen with longer periods of observation after transplantation. Table 5.2 illustrates the comparative results of three studies from our laboratory using similar techniques, in which either fetal or neonatal cells were transplanted into permanent occlusion infarcts. The follow-up after transplantation ranged between 4 weeks and 6–7 months.14,15,18

Left ventricular volumes in systole and diastole were assessed by intravenous ventriculography in vivo. In all these studies, there was a strong tendency to less left ventricular dilation after transplantation of cells. This was most obvious in a study of 4 weeks’ observational time after transplantation.18 When calculating left ventricular ejection fraction, however, there was no difference in this study between the transplant and medium-injected hearts. Interestingly, the other studies with longer follow-up demonstrated a slight and significant improvement in ejection fraction in the cell groups. One might speculate that the longer the time after transplantation the more differentiated are the cells with respect to the “contractile phenotype.” However, we could only speculate about potential mechanisms of increasing ejection fraction in the cell group: 1. Some rare cell-to-cell contacts may have triggered active contraction of the graft in these studies, 2. the grafted cells may also contract independently from the host, 3. contraction of transplanted cells during systole are triggered by wall stress, or 4. the effects observed are solely a consequence of scar thickening and stiffening by the transplanted cells reducing systolic wall stress and on the long-term reducing left ventricular remodeling.

Regional wall motion analysis by ventriculography in the 6-month study mainly revealed that the transplanted group was characterized by less dyskinesia in the area of the scar, which, on the contrary, was a prominent feature in the medium hearts (Table 5.3). Therefore, it was proposed that the main effects of cell transplantation in this

| Table 5.1. Regional myocardial blood flow and capillary density in the infarcted tissue (permanent coronary artery occlusion) four weeks after transplantation of neonatal cardiomyocytes in rats (according to reference 18) |
|-------------------------------------------------|---------------------------------|---------------------------------|
| Regional myocardial blood flow (ml/g/min)       | Scar                            | 0.61 ± 0.11                     |
| Capillary density (perfused capillaries/mm²)    | Scar                            | 125 ± 10                        |
| Capillary density in the graft (perfused capillaries/mm²) | Normal myocardium                  | 1788 ± 83                  |
| Control group                                   | Normal myocardium               | 2.73 ± 0.39                     |
| Transplantation group                           | Scar                            | 0.97 ± 0.18 (p < 0.05)          |
|                                                | Normal myocardium               | 156 ± 62                       |
|                                                |                                 | 1924 ± 114                      |
| Source: According to Reffelmann et al.18        |                                 |                                 |
### Table 5.2
Parameters of left ventricular contractile performance, left ventricular dimensions from intravenous ventriculography, and postmortem morphometric analysis in three studies using a similar rat model of transplantation of immature cardiomyocytes with different periods of follow-up

<table>
<thead>
<tr>
<th></th>
<th>Permanent coronary occlusion, transplantation of neonatal cardiomyocytes, 4 weeks of follow-up</th>
<th>Permanent coronary occlusion, transplantation of neonatal cardiomyocytes, 6 months of follow-up</th>
<th>Permanent coronary occlusion, transplantation of fetal cardiomyocytes, 6–7 months of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic LV volume (µL)</td>
<td>300.9 ± 10.5</td>
<td>256.0 ± 10.4</td>
<td>286.0 ± 26.6</td>
</tr>
<tr>
<td>Systolic LV volume (µL)</td>
<td>174.2 ± 11.1</td>
<td>146.2 ± 8.7</td>
<td>214.8 ± 20.5</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>43.2 ± 1.7</td>
<td>42.6 ± 2.0</td>
<td>25 ± 2</td>
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<tr>
<td><strong>Transplant</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic LV volume (µL)</td>
<td>256.0 ± 10.4</td>
<td>286.0 ± 26.6</td>
<td>417 ± 26</td>
</tr>
<tr>
<td>Systolic LV volume (µL)</td>
<td>146.2 ± 8.7</td>
<td>214.8 ± 20.5</td>
<td>286 ± 27</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>42.6 ± 2.0</td>
<td>36 ± 3</td>
<td>33 ± 2</td>
</tr>
<tr>
<td><strong>Postmortem morphometric analyses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scar thickness (mm)</td>
<td>0.75 ± 0.04</td>
<td>0.93 ± 0.07</td>
<td>0.53 ± 0.07</td>
</tr>
<tr>
<td>Expansion index</td>
<td>0.83 ± 0.06</td>
<td>0.64 ± 0.07</td>
<td>2.41 ± 0.10</td>
</tr>
<tr>
<td>Infarct size (%)</td>
<td>38.2 ± 2.2</td>
<td>36.0 ± 2.5</td>
<td>31.5 ± 1.7</td>
</tr>
<tr>
<td>LV, left ventricular.</td>
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</tbody>
</table>

*Significant versus control group.
study were attributable to a (maybe passive) stiffening of the infarcted area with less bulging during systole and by reducing left ventricular dilation during the remodeling process.

Additionally, morphometric analyses confirmed the (to a certain extent unexpected) beneficial effect on left ventricular remodeling. The scars after cell transplantation were significantly thicker (in all three studies) and this resulted (together with less left ventricular dilation) in a significant reduction of infarct expansion [see table, infarct expansion index according to Hochman and Choo,44 summarizing infarct thinning and left ventricular dilation in one index; Figures 5.1 and 5.4 (see color section)]. One might conjecture that stiffening and thickening the infarcted wall by grafting the cells results in reduced wall stress, thereby leading to less ventricular dilation and remodeling after myocardial infarction.

Thus, cell transplantation exhibited a significant effect on left ventricular performance in these studies, but the main effect of cell transplantation seemed to be the result of less dilation, and favorable effects on the remodeling process. Even if ejection fraction was improved in the studies with longer follow-up, synchronous and effective contractions could not be proven in these investigations.

Similarly, results were observed in a permanent coronary occlusion model with extensive scarring, where scar thinning and left ventricular dilation was prevented by transplantation of fetal cardiomyocytes.35 Importantly, a study in which fetal cardiomyocytes were transplanted 4 weeks after coronary artery ligation, a period in which major steps of ventricular remodeling have already developed, did not show reversal of the remodeling process.45 Nonetheless, the type of cell (fibroblasts or contractile cells) seems to be important with respect to the efficacy, as suggested in comparative studies of various cell types.46,47

Therefore, cell therapy, a treatment strategy initially developed from the cardiocirculatory model of heart failure and aimed at enhancing contractile systolic force, surprisingly exhibited its most convincing effects by reducing remodeling and progression of heart failure over time in these studies, a characteristic of therapies derived from the progressive-neurohumoral model of cardiac failure.

However, another experimental study using infarcted mouse hearts demonstrated pronounced improvement of echocardiographic parameters after transplantation and higher force development, as measured in isolated muscle strips.48 Additionally, a preserved electrical excitability of the transplanted cells was shown, and the authors suggested that direct development of contractile force was the main mechanism of improved ventricular performance.

Interestingly, a study using skeletal myoblast transplantation demonstrated less left ventricular dilation along with increased ex vivo parameters of systolic force, which mainly seemed to be attributable to favorable effects on the remodeling process rather than active systolic contractions.49 Similarly, investigations on transplantation of embryonic and mesenchymal stem cells were performed, and differential effects on remodeling, active force development, and also enhancement of angiogenesis, which also may contribute to improved healing of the scar and favorable effects on remodeling, remain to be evaluated.49,50,51

### Table 5.3. Regional wall motion analysis from intravenous ventriculograms in a rat model of permanent coronary occlusion six months after intramyocardial injection of neonatal cardiomyocytes or medium

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Transplantation group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zone of dyskinesia</td>
<td>55.1 ± 7.3</td>
<td>29.5 ± 8.3*</td>
</tr>
<tr>
<td>(% of infarct)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zone of dyskinesia</td>
<td>24.4 ± 3.9</td>
<td>11.1 ± 3.3*</td>
</tr>
<tr>
<td>(% of perimeter)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Significant versus control group.

**Source:** Modified according to Müller-Ehmsen15; data from a lateral projection of intravenous ventriculography. Dyskinesia, zone of paradoxic systolic movement of the endocardium.

### Symptoms of Heart Failure, Exercise Capacity, and Survival: The Parameters to Decide for or Against Cell Therapy

Cell therapy has the potential to exhibit favorable effects on left ventricular remodeling and performance, and there are many clinical and experimental studies suggesting that this might transfer into improvement of symptoms and survival. However, there are only a few studies...
addressing these issues in experimental investigations. Indeed, most frequently used models of coronary artery ligation (e.g., in the rat, in the mouse) do not result in a high percentage of animals that develop clinically overt heart failure. The study by Roell et al.,48 performed in a mouse model of coronary artery ligation, which reported a pronounced increase in echocardiographic parameters of left ventricular performance after cardiomyocyte transplantation, also reported a marked improvement in survival after cell transplantation. However, most of the animals in the control group died early after transplantation, and the follow-up was relatively short in this study. Jain et al.49 reported an improvement of exercise capacity after transplantation of skeletal myoblasts parallel to favorable remodeling effects. Other studies examined effects on diastolic function, which may equally contribute to symptoms and capacity to exercise.52 Importantly, Pouzet et al.53 investigated whether beneficial effects might occur in addition to angiotensin-converting enzyme inhibition, which is especially important for the translation into clinical practice. Any new therapy for heart failure will be tested against a control group of best medical treatment according to the current state of medical therapy. In their experimental study, they found an additional effect of cell therapy with angiotensin-converting enzyme inhibitors. Apart from this, studies addressing these important questions are rare, but will become most relevant in the phase of clinical testing.

Heart Failure Attributed to Systolic Contractile Dysfunction

Especially when talking about potential clinical applications, we must emphasize that using the term “heart failure” in this chapter as well as in many publications on these topics is a simplification, which needs to be specified. The first step in evaluating a patient with clinical signs of heart failure is undoubtedly a detailed search for potential causes, including valvular heart disease, diastolic dysfunction, pericardial effusion, restrictive filling pattern, etc., any of which may require specific treatment. The majority of studies on cellular cardiomyoplasty (and also on medical treatment) were aimed at cardiac failure attributed to regional systolic left ventricular dysfunction. In the clinical realm, regional systolic dysfunction will be most frequently the consequence of myocardial infarction. In experimental investigations, coronary artery ligation, temporary coronary artery occlusion, or even epicardial application of cryoinjury to the left ventricle have been used to mimic this situation. There are also some experimental investigations using models of dilated cardiomyopathy for the evaluation of cell therapy. All these models may be adequate for studying the basic mechanisms and the overall potential of the technique. However, when transferring the results to the patient with heart failure, the terminology will need to be used more precisely, and (among others) a clear differentiation between systolic and diastolic dysfunction, global and regional contractile dysfunction, as well as ischemic and nonischemic cardiac disease will be necessary when estimating the therapeutic potential of cell therapy.

Summary

Cell therapy is a relatively novel approach to the treatment of heart failure. Although the initial aims of completely rebuilding scarred myocardium by contractile tissue, thereby completely restoring cardiac pumping capacity, have not yet been accomplished, many experimental studies reported beneficial effects on left ventricular performance, most of them attributed to less ventricular dilation, scar thickening, and reduction of infarct expansion. Synchronous beating of the graft in the infarcted territory with the host has not been undoubtedly proven, although it seems to be likely that effective cell-to-cell coupling between the host and graft with propagation of calcium transients and in consequence propagation of contraction is possible after transplantation. A major obstacle in completely restoring regional contractile force seems to be the incomplete integration of the graft into the host and the separation from host cells by connective tissue and the scar. For effectively restoring regional contractile function, this will be the most important issue to be solved.

Nonetheless, transplantation appears to exhibit beneficial effects on myocardial performance that can at least in part be ascribed to less ventricular remodeling. Thus, it is likely
that progression of heart failure over time can be attenuated to a certain degree by cell therapy. Paradoxically, the fundamental idea of restoring pumping capacity of the heart by cell therapy originates in a cardiocirculatory model of cardiac failure, but many effects of cellular cardiomyoplasty may be attributed to beneficial effects on the remodeling process of the ventricle, resembling other therapeutic approaches derived from a progressive model of heart failure.

Whether less ventricular dilation and less infarct expansion translate into better outcome over time and survival, improved symptoms, and exercise capacity remains to be investigated. Most importantly, for potential clinical applications, cell therapy will need to be compared with the best medical and interventional treatment strategies when evaluating its potential benefit for the patient with heart failure.

References

28. Sheilk F, Fandrich RR, Kardami E, et al. Overexpression of long or short FGFR-1 results in FGF-2-mediated...


