The pathogenesis and treatment of cardiac atrophy in cancer cachexia

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Murphy KT. The pathogenesis and treatment of cardiac atrophy in cancer cachexia. Am J Physiol Heart Circ Physiol 310: H466–H477, 2016. First published December 30, 2015; doi:10.1152/ajpheart.00720.2015.—Cancer cachexia is a multifactorial syndrome characterized by a progressive loss of skeletal muscle mass associated with significant functional impairment. In addition to a loss of skeletal muscle mass and function, many patients with cancer cachexia also experience cardiac atrophy, remodeling, and dysfunction, which in the field of cancer cachexia is described as cardiac cachexia. The cardiac alterations may be due to underlying heart disease, the cancer itself, or problems initiated by the cancer treatment and, unfortunately, remains largely underappreciated by clinicians and basic scientists. Despite recent major advances in the treatment of cancer, little progress has been made in the treatment of cardiac cachexia in cancer, and much of this is due to lack of information regarding the mechanisms. This review focuses on the cardiac atrophy associated with cancer cachexia, describing some of the known mechanisms and discussing the current and future therapeutic strategies to treat this condition. Above all else, improved awareness of the condition and an increased focus on identification of mechanisms and therapeutic targets will facilitate the eventual development of an effective treatment for cardiac atrophy in cancer cachexia.

cardiac cachexia; cancer cachexia; cardiac dysfunction; cardiac atrophy; cardiomyopathy

CANCER CACHEXIA IS A complex, multifactorial syndrome characterized by a progressive loss of skeletal muscle mass that cannot be fully reversed by conventional nutritional support and is associated with significant functional impairments (38). The devastating consequences of cachexia include decreased mobility and enhanced fatigue leading to a reduction in quality of life (1), reduced response to chemotherapy (4), and increased mortality. Cachexia affects 40–80% of all advanced cancer patients with the highest prevalence in pancreatic, gastric, and esophageal cancer (13, 39, 103). It is also evident in patients with advanced prostate, head/neck, liver, osteosarcoma, colorectal, cervical, ovarian, lung, and breast cancer (42, 103). Although cachexia is estimated to account for 20–30% of all cancer-related deaths (108), this has not been clinically confirmed, possibly because of difficulties demonstrating causality of the cachexia-death association (54). However, weight loss and body mass index are predictors of survival in cancer patients (70, 96, 97). Weight loss in cancer cachexia involves skeletal muscle and often fat mass, as well as multiple tissues including the brain, gastrointestinal tract, liver, kidney, lung, and heart (6, 55). The cardiac alterations occurring in cancer cachexia may be due to underlying heart disease exacerbated by treatment, the cancer itself, or problems initiated by the cancer treatment (36), and unfortunately, it remains largely underappreciated by clinicians and basic scientists. Clinically, the term “cardiac cachexia” generally refers to the unintentional weight loss caused by heart disease. However, in the field of cancer cachexia, cardiac cachexia describes the cardiac atrophy, remodeling, and dysfunction associated with cancer. It is the latter definition that serves as the basis of this research review. Since an in-depth analysis of each of these processes is beyond the scope of this review, the focus here is on the atrophy component of cardiac cachexia and primarily on the current and future therapeutic strategies to treat cardiac atrophy in cancer cachexia.

Cardiac Atrophy in Cancer

Cardiovascular complications are commonly found in cancer patients (120) and have been shown to be the main causes of death of colorectal cancer patients following elective and nonelective colorectal resection (66). This is not a sole consequence of preexisting cardiac disease with cardiac causes of death in 13.5 (30 days after elective resection) to 5.7% (1-year postoperation) of patients aged 65 yr or younger (with 5.2% having preexisting cardiac comorbidity), but in the general population, only 0.4–0.5% of deaths in the same age group are due to heart disease (66). The same trend was also seen in patients aged 85 yr or older and indicates that cancer patients have an increased cardiac mortality (66). Unfortunately, there is a lack of clinical data on the incidence of cardiovascular complications in cancer patients, and a contributing factor to this has been underdiagnoses with the focus primarily being on treating the malignancy. Another challenge in this field has been determining the relative contribution of underlying heart disease unrelated to cancer compared with that induced by cancer itself and/or the cardiotoxic effects of cancer therapy on...
the pathogenesis and epidemiology of cardiac cachexia in cancer (120). Regarding the latter, numerous excellent reviews have discussed the cardiotoxicity and cardiac side effects of various cancer therapies (21, 35–37, 120) and so will only be briefly discussed here.

It is well established that many anticancer therapies including classic chemotherapeutic agents cause cardiotoxic side effects in a subgroup of patients (2, 35, 119). The incidence of cardiotoxicity differs between agents and is thought to be underreported but may occur in >20% of patients treated with fluorouracil, doxorubicin, or daunorubicin (87). Symptoms include systolic dysfunction and signs associated with heart failure such as tachycardia and S3 gallop (2, 35, 119). Unfortunately, these effects are not limited to chemotherapy drugs, and it was with relative surprise that some targeted anticancer therapies which are tailored to the genetics of each cancer were also found to induce adverse cardiovascular side effects in patients (21). Targeted therapy has mainly involved inhibiting one or more receptor or nonreceptor tyrosine kinases or serine/threonine kinases via administration of monoclonal antibodies or small molecules. Although this approach has dramatically improved antitumor activity, it has also been associated with left ventricular (LV) dysfunction, conduction abnormalities, hypertension, myocardial injury, and heart failure (21, 22). In contrast to the anthracycline and fluorouracil anticancer drugs, there is some evidence that the cardiovascular side effects of tyrosine kinase inhibitors may be reversible, although this remains inconclusive (22, 105).

The coexistence of cardiovascular disease and cancer affects the treatment, as therapy for one may exacerbate the other (120). Since cardiotoxicity limits the effectiveness of anticancer therapies, treatment of cardiac cachexia could improve the response to chemotherapy and enhance the chances of survival. Furthermore, treatment guidelines for cardiovascular disease have typically been made on patients without cancer and so may not be applicable for those with cancer (120). As a consequence, studies examining the efficacy of different treatments for patients with both cardiovascular complications and cancer are desperately needed.

The presentation of patients with cardiovascular complications arising from the cancer itself can vary considerably between patients, but a recent study found that patients with gastrointestinal, pancreatic, and nonsmall cell lung cancer who died from cardiac cachexia had reduced heart mass and LV remodeling, including LV wall thinning and increased fibrosis, compared with those of noncachectic cancer patients and controls (101). Similar cardiac remodeling and dysfunction are evident in Colon-26 (C-26) tumor-bearing mice and Yoshida-130 tumor-bearing rats, two of the most commonly used rodent models of cancer cachexia. In these models, this manifests as an early atrophy of the LV followed by remodeling, including thinning of the septal and interventricular walls and chamber dilation (25, 101, 106, 107). In the later stages of experimental cancer cachexia, systolic and diastolic dysfunction become evident and are followed by increased fibrosis and, in the most severe cases, heart failure (25, 101, 106, 107, 118). Since interventions are typically most successful when initiated early in disease progression, it is of interest to examine the potential mechanisms underlying the early cardiac atrophy associated with cancer. Understanding the mechanisms will help to identify potential therapeutic targets.

**Pathogenesis of Cardiac Atrophy in Cancer Cachexia: Protein Metabolic Imbalance**

As discussed above, cardiac atrophy in cancer may be a consequence of the cancer itself, underlying heart disease unrelated to cancer but exacerbated by treatment and/or the cardiotoxic effects of cancer therapy. Many excellent reviews have discussed the pathogenesis of cardiotoxicity induced by anthracycline and fluorouracil anticancer drugs as well as targeted cancer therapies (35–37, 58, 120) and so will not be a focus here. Instead this section will focus on the pathogenesis of cardiac atrophy that is a consequence of the cancer itself. This is still being elucidated, and since very few studies have been performed in humans, we rely on findings from animal models to inform our understanding of the area. Currently, protein metabolic imbalance is viewed as one of the main mediators of cardiac atrophy in cancer cachexia.

The size of the heart is governed by the relative rates of protein synthesis and degradation, but unfortunately there is a dearth of studies directly measuring these rates in preclinical models of cancer cachexia, and so we currently make inferences based on analysis of the synthesis and degradation signaling pathways (Fig. 1). However, signaling pathways do not necessarily reflect the metabolic pathways, and so it is essential that studies undertake direct analysis of protein synthesis and degradation rates to improve our understanding of this area.

In the only study thus far to have directly measured protein synthesis rates in hearts from animals with cancer cachexia, Ap mice that develop intestinal tumors were found to have an ~70% reduction compared with control C57BL/6 mice (67). This was associated with decreased phosphorylation of mammalian target of rapamycin (mTOR), S6 ribosomal protein, and eukaryotic initiation factor 4E binding protein-1 (4E-BP1), supporting suppression of the protein synthesis pathway in the Apc mice model of cancer cachexia (67). Interestingly, the reductions in mTOR/S6/4E-BP1 in this study occurred in the face of elevated Akt (protein kinase B) phosphorylation (67), but studies have found that IL-6-mediated suppression of this pathway is independent of Akt (90). Cachectic hearts from Apc mice also exhibited increased phosphorylation of 7′-adenosine monophosphate-activated protein kinase (AMPK), which can lead to autophagy and inhibition of mTOR, and is suggestive of increased signaling of degradative pathways (67). However, phosphorylation of Bad (Ser136), which reduces Bad-mediated apoptosis and cell death was increased in Apc mice (67). Taken together, with the fact that despite the large decrease in protein synthesis rate, cardiac mass in Apc mice was only reduced by 6–8%, these findings suggest that protein degradation may actually be decreased rather than increased in cachectic hearts from Apc mice, but direct measurement of protein degradation rates are required to confirm this hypothesis. Suppression of the cardiac protein synthesis pathway has also been implicated in other animal models of cancer cachexia, with hearts from cachectic AH-130 tumor-bearing rats exhibiting reduced expression of insulin and insulin-like growth factor-I receptors and decreased phosphorylation of Akt, glycogen synthase kinase 3α, and 4E-BP1 (101). It therefore appears that at least in the Apc mouse model, decreased protein synthesis and not increased protein degradation is the likely
In cancer cachexia, the ubiquitin-proteasome system (UPS) and autophagy pathways are activated, leading to protein degradation and the loss of myofibrillar proteins in the heart. This occurs in association with an inflammatory state, and proinflammatory cytokines such as interleukin-6 (IL-6) bind to their receptors to initiate a cascade that includes the activation of glycogen synthase kinase 3 (GSK3), leading to the inhibition of Akt, which normally promotes the phosphorylation and inhibition of the forkhead box 01 (FoxO) family of transcription factors. This enables FoxO to translocate to the nucleus and regulate the expression of genes including the ubiquitin ligases muscle ring finger-1 (MuRF-1) and atrogin-1/MAFb, leading to increased protein degradation. Smad2/3 phosphorylation can also inhibit Akt, and in association with the cofactor Smad4, Smad2/3 translocate to the nucleus to regulate the expression of numerous genes that leads to overall protein degradation. Smad2/3 phosphorylation can also inhibit Akt, relieving the phosphorylation and inhibition that Akt normally plays on the forkhead box 01 (FoxO) family of transcription factors. This enables FoxO to translocate to the nucleus and regulate the expression of genes including the ubiquitin ligases muscle ring finger-1 (MuRF-1) and atrogin-1/MAFb, leading to increased protein degradation. Insulin signaling via the insulin receptor (IGFR) is also decreased in cancer, to translocate to the nucleus and regulate the expression of genes including the ubiquitin ligases muscle ring finger-1 (MuRF-1) and atrogin-1/MAFb, enabling nuclear translocation of the transcription factor nuclear factor (NF)-κB to promote the phosphorylation and subsequent degradation of IκB, enabling nuclear translocation of the transcription factor nuclear factor (NF)-κB and the subsequent expression of genes involved in protein degradation. Another potent activator of NF-κB is the inflammatory cytokine tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK), which signals via the Fn14 receptor, and local and circulating levels of TWEAK are increased in cancer. Expression of the transforming growth factor (TGF)-β ligand myostatin is also elevated in cancer. Myostatin binds to the activin type II receptor (ActRIIB), leading to activation of the type I receptors ALK4/5 and phosphorylation of the intracellular Smad2/3. In association with the cofactor Smad4, Smad2/3 translocate to the nucleus to regulate the expression of numerous genes that leads to overall protein degradation. Smad2/3 phosphorylation can also inhibit Akt, relieving the phosphorylation and inhibition that Akt normally plays on the forkhead box 01 (FoxO) family of transcription factors. This enables FoxO to translocate to the nucleus and regulate the expression of genes including the ubiquitin ligases muscle ring finger-1 (MuRF-1) and atrogin-1/MAFb, leading to increased protein degradation. Insulin signaling via the insulin receptor (IGFR) is also decreased in cancer, causing a further inhibition of Akt. This prevents activation of mammalian target of rapamycin (mTOR) and subsequent phosphorylation of protein S6 kinase (S6K) and eukaryotic translation initiation factor 2 (eIF2) and a reduction in protein synthesis initiation factor 2 (eIF2). There is evidence that cancer is associated with increased phosphorylation of S6 kinase, leading to increased autophagy. Autophagy is a process that leads to the degradation of cytoplasmic organelles and proteins, and the presence of double-membraned autophagic vacuoles containing portions of cytoplasm, mitochondria, and myelin-like structures has been observed in cancer cachexia. This process is mediated by the ubiquitin-proteasome system (UPS) and the autophagy/LC3-II, cathepsin L, and beclin pathways. The involvement of the ubiquitin proteasome system (UPS) in the etiology of cardiac atrophy in cancer cachexia remains unclear with one study reporting increased expression of the E3 ubiquitin ligases muscle ring finger-1 and atrogin-1 (muscle atrophy F-box) and higher levels of ubiquinated proteins in the hearts of C-26 tumor-bearing mice (106), but another finding no change in these parameters compared with healthy control mice (25). The opposing findings may be due to the transient pathoetiologic factor contributing to cardiac atrophy. However, enhanced proteolysis may also contribute to the reductions in protein synthesis with E3 ubiquitin ligases shown to target protein initiation factors in skeletal muscle atrophy (59). Whether a similar effect is seen in the heart is not known. Furthermore, while increased protein degradation may not be a major contributor to the cardiac atrophy in these models, it may play a greater role in other cancer models.

Each of the autophagy/lysosome, ubiquitin proteasome, and apoptosis/caspase proteolytic systems leading to protein degradation may be involved in the loss of myofibrillar proteins in cachectic hearts. Consistent with the increased AMPK phosphorylation, markers of autophagy including LC3-II, cathepsin L, and beclin were elevated in cachectic hearts from tumor-bearing rodents, and electron microscopy has revealed the presence of double-membraned autophagic vacuoles containing portions of cytoplasm, mitochondria, and myelin-like structures (25, 67, 101).

The involvement of the ubiquitin proteasome system (UPS) in the etiology of cardiac atrophy in cancer cachexia remains unclear with one study reporting increased expression of the E3 ubiquitin ligases muscle ring finger-1 and atrogin-1 (muscle atrophy F-box) and higher levels of ubiquinated proteins in the hearts of C-26 tumor-bearing mice (106), but another finding no change in these parameters compared with healthy control mice (25). The opposing findings may be due to the transient...
nature of changes in this system with cachectic hearts from AH-130 tumor-bearing rats having increased activity of the UPS on day 11, but reduced activity on days 5 and 13 compared with controls (101). The nuclear factor-κB (NF-κB) transcription factors are well-known regulators of the UPS, and supporting activation of this system as a mediator of cardiac atrophy in cancer is an enhanced expression of the NF-κB p50 and p65 subunits in hearts from a rat model of mammary tumorigenesis (86).

Another process that differentially changes with the progression of cardiac cachexia in cancer is apoptosis, with AH-130 tumor-bearing rats exhibiting an early (day 5) decrease in cardiac caspase-3 activity and a later (days 11 and 13) increase in cardiac caspase-3 activity compared with sham-operated controls (101). Similarly, cardiomyocyte caspase-3 activity was not different from controls at day 15 but reduced significantly at day 27 in C-26 tumor-bearing mice (25).

The molecular signals responsible for these events are still being determined but are likely to involve the increased inflammatory state associated with tumor bearing. Proinflammatory cytokines such as IL-6 and its receptors were found to be increased in cachectic hearts from C-26 tumor-bearing mice (106) and activate a host of intracellular pathways including NF-κB as well as mitogen-activated protein kinase and caspases. Another potent activator of NF-κB is the inflammatory cytokine tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK) that signals via the Fnl4 receptor and was increased in hearts from rats with mammary tumorigenesis (86). Myostatin, a ligand of the transforming growth factor-β (TGF-β superfamily of proteins) has also been implicated as the expression of myostatin, and one of its downstream signaling proteins p-Smad3 were increased in the cachectic hearts of AH-130 tumor-bearing rats (86, 101). Furthermore, TGF-β released from bone due to metastasis-induced bone destruction was recently shown to cause significant skeletal muscle weakness (115). This was due, at least in part, to enhanced oxidation of the ryanodine receptor-1 causing an increase in sarcoplasmic reticulum Ca2+ leak and a subsequent reduction in intracellular signaling required for muscle contraction (115). Whether a similar mechanism occurs in cardiac muscle atrophy associated with bone metastasis is not known, but TGF-β1 has been shown to regulate ryanodine receptor-mediated sarcoplasmic reticulum Ca2+ oscillations in cardiac myocytes (78).

The heart is not spared during malnutrition (19, 45), but nutritional supplementation can reverse the cardiac atrophy (49), suggesting a direct link between energy balance and the regulation of heart size. The mechanisms involved in this effect are still being elucidated, but experiments in mouse hearts showed the starvation-induced cardiac atrophy involved a reduction in ATP and subsequent activation of AMPK, leading to autophagy and inhibition of mTOR signaling (111). These effects were insulin-like growth factor-I dependent. Since anorexia significantly contributes to the pathogenesis of cancer cachexia, it is possible that a mechanism similar to that induced with starvation is involved in the cardiac atrophy in cancer cachexia, but this has yet to be tested.

Mitochondrial dysfunction associated with impaired energy supply is also a likely contributor to the cardiac atrophy in cancer cachexia, with mitochondrial content and function being important mediators of striated muscle size. Skeletal muscles from cachectic tumor-bearing mice had reduced ATP synthesis rates and increased mitochondrial uncoupling (113), as well as NF-κB- and mitogen-activated protein kinase-dependent mitochondrial dysfunction (40). Furthermore, both skeletal muscles and hearts from Yoshida AH-130 tumor-bearing rats exhibited increased oxidation of proteins involved in glycolysis, ATP production and distribution, muscle contraction, and mitochondrial function (69). Anticancer treatments also have potent effects on mitochondrial function in the heart with doxorubicin-mediated cardiac toxicity in mice shown to be due, at least in part, to p53-mediated oxidative stress (114). Another study employed a novel mitochondrial-targeted antioxidant and a selective calpain inhibitor to demonstrate that doxorubicin-induced atrophy and dysfunction of skeletal and cardiac muscles involved increased mitochondrial reactive oxygen species production and calpain activation (73). These findings indicate that mitochondrial dysfunction caused by both cancer and its treatments contributes to the atrophy of skeletal and cardiac muscle, and therefore the mitochondria represents a promising therapeutic target for the treatment of skeletal and cardiac muscle cachexia in cancer. This notion provides further support for the development of therapies that target cell-specific mitochondria (27).

Despite recent major advances in the treatment of cancer, little progress has been made in the treatment of cardiac cachexia, and much of this is due to lack of information regarding the mechanisms. Improving our understanding of the mechanisms leading to cardiac atrophy in cancer will help identify new therapeutic targets and hopefully lead to an effective treatment.

Current Treatment of Cardiac Atrophy in Cancer Cachexia

The best way to treat cardiac cachexia in cancer is to cure the cancer. However, this is rarely achieved, and even when successful, cardiomyopathy has generally worsened in the interim. There are currently no Food and Drug Administration-approved drugs for cardiac cachexia in cancer, and to date, no known clinical trials have specifically targeted this aspect of cancer. However, several therapies have been tested in preclinical models, including NF-κB inhibitors, activin receptor antagonists, β2-adrenoceptor agonists, and drugs used to treat heart failure like β-blockers, aldosterone antagonists, and angiotensin-converting enzyme (ACE) inhibitors. The benefit of using established cardiovascular drugs is that the translation from animal experiments to clinical use could be rapid. A list of current therapeutic approaches to treating cardiac cachexia in cancer are summarized in Table 1, and their efficacy is detailed below.

ACE inhibitors. The classical renin-angiotensin system (RAS) axis involves the conversion of angiotensin I (ANG I) to angiotensin II (ANG II) by the ACE. ANG II signals via the ANG II type 1 receptor (AT1) to elicit effects in different tissues including well-known effects in smooth muscle such as vasoconstriction. As a consequence, ACE inhibitors and AT1 antagonists are used widely to treat hypertension. ACE inhibitors have also been shown to slow the progression of LV dysfunction in various cardiomyopathies (63) and to prevent cardiotoxicity and improve cardiac function in patients receiving chemotherapy (18). Their efficacy for attenuating cardiac cachexia has been evaluated in several preclinical models but has produced conflicting results. Treatment of tumor-bearing...
rats with the ACE inhibitor imidapril did not improve LV remodeling, cardiac function, or survival (101), and we found in C-26 tumor-bearing mice that despite reducing tumor size and inducing large improvements in locomotor activity and skeletal muscle fatigability, the ACE inhibitor perindopril did not protect against cardiac atrophy and actually exacerbated it (76). Furthermore, perindopril did not prevent the large decrease in cardiac α-myosin heavy chain mRNA expression in severely cachetic mice, which is typically associated with cardiac dysfunction (74). However, a recent study showed that the AT1 antagonist losartan prevented the reductions in fractional shortening, ejection fraction, stroke volume, and posterior wall thickness and attenuated the increase in LV end-diastolic diameter during systole in C-26 tumor-bearing mice (102). Losartan treatment for 18 days also attenuated the decrease in systolic blood pressure and developed pressure and reduced tumor size in cachetic mice (102). The greater efficacy of AT1 antagonism compared with ACE inhibition has important implications for the pathogenesis of cardiac cachexia in these preclinical models. By blocking the production of ANG II, ACE inhibitors reduce activation of both the AT1 and ANG II type 2 (AT2) receptors and decrease bradykinin breakdown, resulting in activation of the B1 and B2 receptors for bradykinin. In comparison, AT1 antagonism results in increased ANG II levels and activation of AT2, which causes a small increase in bradykinin (50). Thus the protective effect of losartan compared with the lack of effect of imidapril and perindopril suggests that activation of the AT2 may be beneficial for attenuating cardiac cachexia in these preclinical models. AT2 activation counteracts many of the detrimental effects of AT1 signaling and in the heart has been shown to induce vasodilation, reduce pathological remodeling, and improve cardiac function in animal models of hypertension (24), myocardial infarction (82), and ischemia-reperfusion injury (57). Importantly, AT2 expression is much higher in human hearts than rodent hearts (112), and AT2-mediated actions are therefore likely enhanced in humans (71), supporting the clinical potential of AT2 activation induced using AT1 antagonists or AT2 agonists for treating cardiac cachexia in humans; however, this remains to be tested.

Another strategy may be to target the alternative RAS axis, which involves the conversion of ANG I to ANG-(1–7) via two pathways: 1) direct hydrolysis of ANG II to ANG-(1–7) via ACE2 and 2) indirect hydrolysis of ANG I to ANG-(1–9) via ACE2 and the subsequent conversion of ANG-(1–9) to ANG-(1–7) via ACE. ANG-(1–7) signaling is mediated through the mitochondrial assembly receptor (MasR), and signaling via this pathway has cardioprotective effects including improving LV remodeling and function in rodent models of diabetic cardiomyopathy (32) and myocardial infarction (29, 121). However, the clinical benefits of targeting this pathway in cardiac cachexia in cancer have yet to be examined.

Activin type II receptor antagonists. Myostatin, a member of the TGF-β superfamily of proteins, is a well-known negative regulator of skeletal and cardiac muscle mass (72, 95). Experimental models of cancer cachexia have been shown to exhibit

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### Table 1. Therapies trialled for treating cardiac cachexia in preclinical models of cancer cachexia

<table>
<thead>
<tr>
<th>Target of Action</th>
<th>Drug</th>
<th>Animal Model</th>
<th>Findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor</td>
<td>Imidapril</td>
<td>AH-130 rats</td>
<td>Did not improve LV remodeling and dysfunction.</td>
<td>(101)</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>Perindopril</td>
<td>C-26 mice</td>
<td>Exacerbated the reduction in heart mass.</td>
<td>(76)</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>Losartan</td>
<td>C-26 mice</td>
<td>Increased FS, EF, SV, and posterior wall thickness; reduced LV end-diastolic diameter during systole; and increased systolic BP and developed pressure.</td>
<td>(102)</td>
</tr>
<tr>
<td>Activin type II receptor antagonists</td>
<td>Soluble activin receptor IIIB</td>
<td>C-26 mice</td>
<td>Increased heart mass.</td>
<td>(122)</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>Spironolactone</td>
<td>AH-130 rats</td>
<td>Increased FS, EF, SV, end-diastolic diameter and volume, cardiac output, and LV mass.</td>
<td>(101)</td>
</tr>
<tr>
<td>β1-agonist</td>
<td>Bosiprol</td>
<td>AH-130 rats</td>
<td>Increased LV end-diastolic diameter, SV, LV mass, and total heart mass and reduced heart rate</td>
<td>(101)</td>
</tr>
<tr>
<td>β2-agonist</td>
<td>Formoterol</td>
<td>AH-130 rats</td>
<td>Higher dose (2 mg/kg) increased heart mass; low dose (0.3–1.0 mg/kg) did not improve heart mass. Low dose (0.3 mg/kg) increased LV volume and diameter during diastole, SV, LV mass, and reduced posterior wall thickness.</td>
<td>(15, 56, 109)</td>
</tr>
<tr>
<td>β2-agonist</td>
<td>Formoterol</td>
<td>LLC mice</td>
<td>Increased heart mass (2 mg/kg).</td>
<td>(15)</td>
</tr>
<tr>
<td>3-HMG CoA reductase inhibitor</td>
<td>Anti-Fn14 antibodies</td>
<td>C-26 mice</td>
<td>Increased heart mass.</td>
<td>(52)</td>
</tr>
<tr>
<td>5-HT1A receptor agonist</td>
<td>Tandospiron</td>
<td>AH-130 rats</td>
<td>Increased heart mass, LV mass, FS, EF, SV, and cardiac output and decreased LV end-systolic diameter.</td>
<td>(33)</td>
</tr>
<tr>
<td>NF-κB agonist</td>
<td>Nemo-binding domain peptide and Compound A</td>
<td>C-26 mice</td>
<td>Increased LV mass, anterior and posterior wall thickness, FS, EF, and cardiomyocyte CSA and decreased cardiac NF-κB activity.</td>
<td>(117)</td>
</tr>
<tr>
<td>PPAR-γ activator</td>
<td>Rosiglitazone</td>
<td>AH-130 rats</td>
<td>Increased FS, EF, SV, cardiac output, and septum diameter during systole and diastole and did not improve heart mass.</td>
<td>(110)</td>
</tr>
<tr>
<td>Non-specific</td>
<td>Resveratrol</td>
<td>C-26 mice</td>
<td>Increased heart mass and LV anterior and posterior wall thickness and decreased LV end-diastolic dimension and cardiac NF-κB activity.</td>
<td>(100)</td>
</tr>
<tr>
<td>Non-specific</td>
<td>Resveratrol</td>
<td>AH-130 rats</td>
<td>Exacerbated the reduction in heart mass.</td>
<td>(16)</td>
</tr>
<tr>
<td></td>
<td>Resveratrol</td>
<td>LLC mice</td>
<td>Did not improve heart mass.</td>
<td>(16)</td>
</tr>
</tbody>
</table>

C-26, Colon-26; LLC, Lewis lung carcinoma; LV, left ventricle; FS, fractional shortening; EF, ejection fraction; SV, stroke volume; BP, blood pressure; ACE, angiotensin-converting enzyme; CSA, cross-sectional area; PPAR-γ, peroxisome-proliferator-activated receptor-γ; 3-HMG CoA, 3-hydroxy-3-methylglutaryl coenzyme A.
elevated myostatin levels (26), and studies by ourselves and others have demonstrated efficacy of systemic myostatin inhibition for attenuating cachexia in tumor-bearing rodents (12, 62, 75). Although early work focused on myostatin produced in skeletal muscle where it functions in an autocrine manner, more recent work has found that myostatin is produced in other tissues including the heart and that myostatin released from cardiomyocytes can induce skeletal muscle wasting in mice (48). Conversely, cardiac-specific myostatin deletion was sufficient to attenuate skeletal muscle wasting in a mouse model of heart failure but surprisingly did not improve fractional shortening or heart mass (48). Heart failure patients have been found to have elevated serum myostatin levels (43), and these findings suggest that increased cardiac production of myostatin in pathological conditions can regulate skeletal muscle mass in an endocrine-like manner. As a consequence, cardiac-specific myostatin inhibition appears a promising therapy for treating skeletal muscle wasting in conditions associated with elevated serum myostatin levels, but this has yet to be tested in cancer cachexia.

More recently, activin A, another TGF-β ligand that binds the same transmembrane receptor as myostatin, the activin type II receptor (ActRIIB), has been shown to have even greater potency than myostatin for inducing skeletal muscle atrophy (20). Therefore, studies have investigated the therapeutic potential of inhibiting signaling of both myostatin and activin via the use of soluble recombinant ActRIIB and other “ligand traps” for improving skeletal and cardiac mass in various diseases including cancer cachexia (122). Treatment of C-26 tumor-bearing mice with soluble recombinant ActRIIB improved survival and prevented the loss of body weight by increasing skeletal muscle and heart mass without affecting tumor size (122). However, the therapeutic potential of ActRIIB antagonism and “ligand traps” was questioned when a clinical study in children with muscular dystrophy was terminated because of side effects including unwanted bleeding (ClinicalTrials.gov identifier: NCT01099761). The side effects were most likely due to effects of other TGF-β ligands on angiogenesis. Furthermore, the clinical potential of ActRIIB antagonism for treating cardiac cachexia needs to be considered in view of a recent paper showing that systemic overexpression of activin A and cardiac-specific knockout of follistatin-like 3, an endogenous extracellular inhibitor of activin A, each protected mice hearts from ischemia-reperfusion injury (84). As a consequence of these findings, current work is focused on the generation of more specific approaches to target ActRIIB, myostatin, activin A, and their downstream signaling pathways including inhibition of the effector proteins Smad2/3 and activation of the endogenous inhibitor Smad7.

**Aldosterone antagonists.** The contribution of aldosterone to the pathophysiology of heart failure is well established, and so aldosterone antagonists (also referred to as mineralocorticoid receptor antagonists) are commonly used to treat patients with heart failure and reduced LV ejection fraction (17). Since aldosterone levels are elevated both in cancer patients who died of cardiac cachexia and in rodent models of cancer cachexia (101) and since cardiac cachexia can often result in heart failure, the therapeutic potential of the aldosterone antagonist spironolactone was investigated in AH-130 tumor-bearing rats (101). Spironolactone improved survival and increased systolic function as evidenced by an improved ejection fraction and fractional shortening (101). Although it did not enhance total heart mass, it did prevent the decreases in LV mass, end-diastolic diameter and volume, stroke volume, and cardiac output (101). The mechanisms by which spironolactone improved the cardiomyopathy of cachectic hearts included a reduction in fibrosis, apoptosis, trypsin-like activity of the UPS, and myostatin protein expression (101). It also enhanced the protein synthesis signaling pathway, with increases in phosphorylation of Akt and 4E-BP1, and elevated myosin heavy chain expression in spironolactone-treated tumor-bearing rats (101). The spironolactone-treated rats also ate more than double that of the untreated tumor-bearing group and had much greater levels of physical activity, supporting the therapeutic value of aldosterone antagonists in cardiac cachexia in cancer.

**β1-Adrenoceptor antagonists.** Bisoprolol is a selective β1-adrenoceptor antagonist (β-blocker) commonly used to treat hypertension, cardiac ischemia, and congestive heart failure. Bisoprolol improved survival, increased total heart mass, and attenuated the decreases in LV mass, end-diastolic diameter and volume, and stroke volume but did not improve systolic function in AH-130 tumor-bearing rats (101). Mechanisms contributing to these effects included a reduction in both trypsin-like activity of the UPS and myostatin expression and an increase in Akt phosphorylation and myosin heavy chain expression (101). Similar to spironolactone, bisoprolol enhanced food intake and activity levels, outcomes that are clinically desirable.

**β2-Adrenoceptor agonists.** β2-Adrenoceptor agonists (β2-agonists) are used clinically to treat asthma because of their bronchodilatory properties, but they also have potent anabolic effects on skeletal muscle (64). Improvements in skeletal muscle mass and function following β2-agonist treatment have been found in preclinical models of sarcopenia (age-related muscle wasting), denervation, muscular dystrophy, sepsis, myotoxic injury, and cancer cachexia (15, 64). However, side effects of β2-agonists have included pathological cardiac hypertrophy, cardiotoxicity, and impairments in cardiac function (64). Since treatment of AH-130 tumor-bearing rats and Lewis lung carcinoma tumor-bearing mice with the β2-agonist formoterol (2 mg/kg) had been shown to increase heart mass (15), a recent study investigated whether formoterol adversely affected cardiac function in AH-130 tumor-bearing rats (109). Despite inducing similar improvements in skeletal muscle mass (+11–15%), a lower dose of formoterol (0.3 mg/kg) did not increase heart mass or alter systolic function but did enhance LV mass and stroke volume (109). However, this was associated with LV remodeling including LV chamber dilation, increased LV volume, and thinning of the posterior wall during systole, which are often predictors of incoming heart failure (109).

**Fn14 inhibitors.** The inflammatory cytokine TWEAK and its receptor Fn14 negatively regulate skeletal muscle growth and function (104). However, recent in vivo studies using pharmacological and genetic modulation of TWEAK and Fn14 have also demonstrated a role for this pathway in the development of pathological cardiac hypertrophy, fibrosis, LV remodeling and dysfunction, and heart failure (31, 51, 81, 85). We recently found that injection of H-Ras V12 oncogene transformed fibroblast cells with a lentiviral construct expressing the human Fn14 receptor into C57BL/6 mice, reduced heart mass, an
effect that was prevented by treatment with an anti-Fn14 antibody (52). Supporting the therapeutic potential of TWEAK/Fn14 inhibition for treating cardiac cachexia, only three injections of an anti-Fn14 antibody was able to completely prevent the reduction in heart mass in C-26 tumor-bearing mice (52). Although TWEAK/Fn14 inhibition has been shown to effectively inhibit fibrosis and prevent LV remodeling and dysfunction in other models of cardiovascular disease, whether similar improvements are seen in cancer needs to be investigated to comprehensively determine the therapeutic potential of TWEAK/Fn14 inhibition for treating cardiac cachexia.

3-Hydroxy-3-methylglutaryl CoA reductase inhibitors. 3-Hydroxy-3-methylglutaryl CoA reductase inhibitors, also known as statins, are used clinically for the treatment of dyslipidemia. In addition to the well-known effects on cholesterol, statins have anti-inflammatory properties, and since inflammation is a prominent feature of cancer cachexia, the effects of simvastatin on cardiac cachexia was investigated in AH-130 tumor-bearing rats (88). Simvastatin improved survival and ejection fraction but not fractional shortening or total heart mass (88). It also attenuated the reduction in LV end-diastolic diameter, stroke volume, and cardiac output. These effects were not due to a reduction in tumor size or to significant improvements in food intake or activity levels, but rather direct effects on the heart. However, given that activity levels are an indicator of an animal’s general health and well being (14, 41), they also suggest that overall health was not improved, which is one of the main goals of cardiac cachexia treatment.

5-Hydroxytryptamine-1A receptor agonists. Since anorexia significantly contributes to the pathogenesis of cancer cachexia, appetite stimulants have been the focus of many studies aiming to treat this condition and may therefore also provide beneficial cardiovascular effects. The 5-hydroxytryptamine-1A (5-HT1A) receptor binds serotonin-1, which has well-known antidepressive effects and can also stimulate appetite. 5-HT1A receptor activation is also involved in central cardiovascular regulation by decreasing sympathetic tone and reducing peripheral vascular resistance (94). As a consequence, the selective 5-HT1A receptor partial agonist tandospirone, which is used clinically in China and Japan as an antidepressant, was investigated for its potential to increase food intake and reduce skeletal and cardiac muscle cachexia in the Yoshida hepatoma rat model (33). Although low-dose tandospirone (1 mg·kg\(^{-1}\)·day\(^{-1}\)) had little effect on weight loss, food intake, locomotor activity, and cardiac parameters compared with placebo controls, high-dose tandospirone (10 mg·kg\(^{-1}\)·day\(^{-1}\)) improved survival, attenuated weight loss, increased food intake, locomotor activity, heart mass, LV mass, systolic function (fractional shortening and ejection fraction), stroke volume, and cardiac output and reduced LV end-systolic volume and diameter (33). While these findings support the potential of 5-HT1A receptor agonists for treating cardiac cachexia, the effective dose was much higher than the clinical dose (~0.4–0.5 mg·kg\(^{-1}\)·day\(^{-1}\)), and so caution needs to be used in the clinical translation of these results.

NF-κB inhibitors. Two novel NF-κB inhibitors targeting the IkB kinase complex, NF-κB essential modifier binding domain peptide and Compound A, were tested for their ability to attenuate cardiac cachexia in C-26 tumor-bearing mice (117). Both drugs inhibited cardiac NF-κB activity and attenuated the reductions in cardiac mass and cardiomyocyte cross-sectional area. Echocardiographic analyses also revealed that they prevented thinning of the anterior and posterior LV walls as well as systolic dysfunction. The effects of compound A were not due to decreases in tumor size, and the effects of NF-κB essential modifier binding domain peptide were independent of changes in the release of tumor-derived compounds.

Peroxisome proliferator-activated receptor-γ activators. Agonists of the nuclear transcription factor peroxisome proliferator-activated receptor-γ (PPAR-γ) are used to improve insulin sensitivity in diseases such as type 2 diabetes mellitus, obesity, and atherosclerosis and have also been shown to improve insulin sensitivity in mice with cancer cachexia (7). One of the targets of PPAR-γ activation is increased transcription of the glucose transporter, and since GLUT4 mRNA expression is reduced in hearts from C-26 tumor-bearing mice (106), PPAR-γ agonists have the potential to improve insulin sensitivity and, consequently, also function in cachetic hearts. Treatment of AH-130 tumor-bearing rats with the PPAR-γ agonist rosiglitazone increased ejection fraction, fractional shortening, LV stroke volume, cardiac output, and septum diameter during systole but did not improve LV mass, total heart mass, end-diastolic diameter, or end-systolic diameter (110). Although these findings indicate some benefits of rosiglitazone for treating cardiac cachexia, they need to be considered in light of its tumultuous clinical history. In 2007, rosiglitazone was linked to an increased risk for adverse cardiovascular events (79) and was subsequently withdrawn from the market of several countries. More recent studies, however, have failed to confirm the cardiovascular risks associated with rosiglitazone, causing the Food and Drug Administration in 2013 to lift some of their specific restrictions on this drug.

Non-specific compounds. Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a phytoalexin produced naturally in response to injury in the skin of plants such as grapes, blueberries, and raspberries. It has been shown to have a multitude of effects including being anti-inflammatory, antioxidative, and cytoprotective. Known targets in the heart include increasing endothelial nitric oxide availability via the estrogen receptor-α and sirtuin-1, having direct and indirect antioxidant properties and reducing the production of reactive oxygen species, inhibiting NF-κB and proinflammatory cytokines including TNF-α, and enhancing insulin sensitivity via AMPK (61, 65). Resveratrol has been shown to have a wide range of health benefits, so it was not surprising that in C-26 tumor-bearing mice, resveratrol reduced NF-κB activity, improved heart mass, and attenuated the LV wall thinning and chamber dilation (100). Despite resveratrol being previously shown to have anticancer effects (8), there was no reduction in tumor size indicating that the cardioprotective benefits were direct effects on the heart (100). However, the cardioprotective effects of resveratrol may be specific to the preclinical model used with treatment of Lewis lung carcinoma tumor-bearing mice having no effect on heart mass and treatment of AH-130 tumor-bearing rats actually exacerbating the reduction in heart mass (16). These conflicting findings highlight the importance of testing the efficacy of potential therapies in different models of cardiac cachexia.

Because polyunsaturated fatty acids of the ω3 series (which are commonly found in fish oil) have potent anticancer effects
Exercise Training for Treating Cardiac Atrophy in Cancer Cachexia

In addition to pharmaceutical intervention, exercise training has been suggested as an effective method for attenuating cancer cachexia (23). The rationale for this is that exercise increases strength and reduces fatigability, which are both impaired in cancer cachexia (3). It is also a powerful stimulus of muscle anabolism (47). Despite exercise currently being the only validated treatment for many conditions of muscle atrophy (23), there have been relatively few preclinical studies and even fewer clinical studies specifically investigating the efficacy of exercise training for attenuating cancer cachexia. The limited clinical studies typically support a positive effect of exercise training for maintaining physical performance (60, 83), but findings from preclinical studies have been difficult to interpret. Aerobic treadmill running improved skeletal muscle mass in tumor-bearing rats (28, 30), and in ApcMUT/MUT mice with IL-6 overexpression, it attenuated the loss of body and muscle mass and improved insulin sensitivity and energy status within the muscle without significantly reducing IL-6 levels (93). Importantly, in these and other preclinical studies, exercise was found to reduce tumor burden (9, 10, 28, 30, 93), and in a recent study, exercise before the implantation of 4T1 cells to model invasive breast cancer reduced tumor burden, an effect attributed at least in part to training-induced changes in energy use (44). While these studies clearly support the therapeutic potential of exercise, other findings have been less supportive. In one study, exercised rats ate less than sedentary tumor-bearing controls and, in the later stages, gained less weight and had reduced fat compared with sedentary rats, indicating that while exercise was initially beneficial for protecting muscle mass, the reduced food intake and accelerated energy demand induced by exercise likely caused an overall greater state of cachexia (30). It was also found that anaemic C-26 tumor-bearing mice subjected to mild endurance training lost more body weight and had less muscle mass than sedentary tumor-bearing mice (5), outcomes that are undesirable in cancer cachexia. An alternative for severely cachectic patients and those that are unable to exercise may be electrical stimulation, where muscle contractions are elicited but the same strains are not placed on the body. Although cachectic ApcMUT/MUT mice were found to have an altered muscle metabolic response following a single bout of low-frequency electrical stimulation (92), they were able to initiate a growth response to seven bouts of high-frequency eccentric muscle contractions (46). Future studies should continue to investigate the efficacy of different protocols of electrical stimulation for treating cancer cachexia.

Despite the well-known cardiovascular benefits of exercise (116) and the ability of exercise to attenuate pathological cardiac remodeling, reduce the risk of hospitalization, and improve quality of life in heart failure patients (98, 116), there is a complete dearth of information regarding its usefulness for treating cardiac atrophy in cancer cachexia. Only one preclinical study has investigated the effects of exercise training on cardiac cachexia, and no clinical study has focused on it. In a rat model of mammary tumororigenesis induced by administration of N-methyl-N-nitosourea, treadmill running had no effect on heart mass but appeared to attenuate the cardiomyocyte disorganization and reduce the interstitial fibrosis observed in sedentary controls, although these observations were not quantified (86). Exercise prevented the increases in cardiac TWEAK, TNF receptor-associated factor-6, atrogin-1, and NF-xB p50 protein expression but also reduced the incidence of mammary lesions, so it is not known whether these findings were due to direct effects on the heart (86).

Given the limited number of studies and conflicting findings, it is apparent that the benefits of exercise training and electrical stimulation on skeletal and cardiac muscle cachexia in cancer still need to be clarified. It is clear, however, that anemia must be resolved before exercise can be initiated (5). Furthermore, there is increasing evidence that exercise is beneficial for attenuating the cardiotoxicity of various anticancer treatments, with aerobic exercise found to reduce oxidative stress and improve systolic function without affecting the antitumor activity of doxorubicin in preclinical models (89, 99). Since fatigue is one of the most disturbing consequences of cancer cachexia and can vary in severity between patients (1), the mode and intensity of exercise training must be tailored to each individual, based on their physical capacities. A combination of resistance and endurance training to improve both the maximum strength and fatigability of muscles may provide the best effects. Furthermore, the nutritional state and anticancer regime of the patient need to be considered to maximize exercise benefits. Thus a multimodal approach is likely required for the best outcomes (5).

Clinical Implications

In interpreting findings from the discussed drug intervention studies, it is important to note potential confounding factors and the limitations of preclinical models. Potential confounding factors include effects on tumor size, food intake, and physical activity levels. While it is of course desirable for interventions to reduce tumor size, it makes it difficult to discern whether any cardiovascular benefits were due to a reduced tumor load or due to direct effects on the heart. Some interventions also caused animals to eat more and have greater levels of physical activity, making it difficult to determine whether any improvements in cardiomyopathy were a consequence of direct effects on the heart, the increased caloric intake, or the beneficial cardiovascular effects of exercise. Nonetheless, food intake and physical activity levels are indicators of overall health and quality of life and from a patient and clinical perspective, interventions improving these parameters have significant therapeutic value.

Most of the information on the pathogenesis and efficacy of potential treatments has come from animal models because of a lack of human data. In fact, only one study has examined cardiac cachexia in human cancer patients (101). While information from preclinical models is essential, it is equally important to acknowledge the limitations of these models. Most
of the models used in cardiac cachexia in cancer research have been those requiring the injection of cancer cells previously obtained from donor animals (i.e., C-26 model), which were exposed to carcinogenic agents and therefore lack the natural tumor development seen in humans (91). Moreover, the tumors express the rodent homologs of human tumor genes, which may impact on the testing of targeted therapies and the translation of results (34). There is also significant variation in tumor and cachexia development between and within rodent strains that can be attributed, at least in part, to differences in laboratory practices relating to cell storage conditions, passage number, and injection site (80). Genetically engineered mouse models such as the ApcMin/+ mouse have also been used in cancer cachexia research, but genetically engineered mouse models can be limited by variability in the incidence of invasive cancers as well as the considerable expense and time required to develop and maintain colonies (34, 91). Another major limitation of these models is that the tumor burden is much greater and develop at a much faster pace than that seen in humans, and therefore tumor-derived factors may not play as important a role in human cardiac cachexia. For example, in our C-26 model, tumor burden represents ~5–8% of total body mass and develops at a rate of 0.3–0.5% total body mass per day. The rapid speed of tumor progression limits the therapeutic window in which treatments can be tested, meaning that only those exerting rapid and substantial effects will be seen to have benefit (91). Furthermore, any potential adverse side effects that take some time to develop may be missed. Many of the models also use solid tumors that do not metastatize in the experimental time frame, whereas in humans, metastases are present at diagnosis in ~20–25% of colorectal cancer patients and develops during the disease in an additional ~20% of patients (68). Metastatic models exhibiting cachexia and representing the advanced stage of disease, such as our model of colorectal liver metastases (77), have been characterized and should be used more frequently to aid in the translation of preclinical research. The relative age of animals used in cancer cachexia studies also differs from the patient population, with rodent experiments typically being initiated at ~4–12 wk of age, corresponding to adolescence, young adulthood, whereas cancer cachexia is most prevalent in the aged population (91). Experiments are also typically initiated in healthy mice with a normal body composition, but with the population becoming more obese and the risk factor paradox of wasting diseases now being recognized (53), it is likely that obese mice may respond differently to treatments. It is clear that in addition to more human studies being carried out in this area, laboratories need to adopt standard preclinical models, protocols and clinically relevant, end-point measures to allow comparisons between studies and to facilitate progress in this area.

Concluding Remarks

Although awareness of cardiac cachexia in cancer has significantly improved in recent years, it remains an understudied area of research, and more focus is required to improve our understanding of the mechanisms so that effective treatments can be identified. Aldosterone antagonists and β-blockers have been shown to attenuate many of the deleterious cardiac effects but did not improve heart function to the level of healthy controls, and so there remains an urgent need to discover new therapeutic targets for cardiac cachexia. New targets that deserve more attention include inhibitors of the TWEAK/Fn14 pathway, 5-HT1A receptor agonists, and inducers of the alternative ACE2/ANG-(1–7)/MasR RAS axis. It is absolutely essential that preclinical studies use multiple models of cachexia to identify efficacy. Improving our understanding of the mechanisms causing cardiac cachexia may help uncover additional new targets. The beneficial effects of exercise training for treating cardiac cachexia still need to be resolved, and it is likely that a multimodal approach including nutritional support, pharmacological intervention, and exercise training will yield the best outcomes. Treatment of cardiac cachexia could potentially reduce the incidence and severity of cancer fatigue syndrome and dramatically improve the quality of life for a large proportion of cancer patients. By the reduction of cardiotoxicity, it could also enhance the response to anticancer treatments and improve the chances of survival. Because many anticancer therapies have dose-limiting cardiotoxic effects, treatment of cardiac cachexia could improve the response to chemotherapy and enhance the chances of survival. To achieve this, however, cardiologists and oncologists need to continue to work together to improve detection and individualize therapies and basic scientists need to continue unravelling the mechanisms so that more effective treatments can be identified.

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REFERENCES


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CARDIAC ATROPHY IN CANCER CACHEXIA


