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Cardiovascular Research 45 (2000) 294–302

Cardiovascular Research

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Review

Angiogenic growth factors: potential new treatment for acute myocardial infarction?

Lino M. Gonçalves*

Cardiology Department, Coimbra University Hospital, 3049 Coimbra Codex, Portugal

Received 2 August 1999; accepted 7 October 1999

Abstract

In models of hind-limb ischemia and progressive coronary artery occlusion, angiogenic growth factor proteins and genes expressing growth factors have been shown to induce the development of collateral vessels and remodeling of existing collaterals. The therapeutic potential of growth factors in the setting of acute myocardial infarction may be related to non-angiogenic properties of growth factors as well, and is the focus of this review. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Collateral circulation; Growth factors; Necrosis

1. Introduction

Acute myocardial infarction (AMI) is a leading cause of death and disability in the Western World. In the United States, 1.5 million people are hospitalized annually with AMI [1], and AMI is responsible for 25% of all deaths [1]. Moreover, a substantial number of AMI survivors are significantly disabled; thus, the social costs of this disease are enormous.

In the last four decades, substantial advances have been achieved in the treatment of AMI. Treatment of potentially fatal arrhythmias in Coronary Care Units [2], infarct size reduction strategies through the introduction of nitrates [3], beta-blockers [4], and surgery [5], and most importantly, thrombolytic agents [6] and direct PTCA [7] have importantly decreased mortality from AMI. These developments have reduced the in-hospital mortality to as low as 3% in selected populations of patients with AMI treated by direct PTCA [7]. Despite the impact of these developments, however, heart failure remains the leading cause of in-hospital morbidity and mortality in AMI patients [8]. Thus, adjunctive therapies for the limitation of infarct size could serve to limit heart failure and advance the treatment of AMI [9].

An interesting hypothesis is that the development of new vessels (angiogenesis) or the remodeling of preexisting collaterals may form natural bypasses that could compensate for the occlusion of an epicardial coronary artery, improving the outcome after AMI.

Several growth factors such as fibroblast growth factors (FGFs) [10,11]. Vascular Endothelial Growth Factor (VEGF) [12,13]. and Insulin Growth Factors (IGFs) [14,15] have angiogenic properties. During recent years, a number of experimental studies have suggested that treatment with angiogenic growth factors can promote the development of collaterals to ischemic tissue in models of progressive coronary occlusion [16–19], and AMI [20–22].

Angiogenic growth factors have been shown to reduce infarct size and improve left ventricular ejection fraction in animal models of AMI [20,23]. The reduction in infarct size was associated with increased vascularity in one study, suggesting that an angiogenic mechanism was operative in reducing infarct size [20]. Nevertheless, it is counterintuitive to suggest that the development of new blood vessels could account for a reduction in infarct size, given the extended time-frame required for vascular growth (days), compared to the limited window of opportunity for myocardial salvage (hours). In addition to their

*Tel.: +351-239-40-0414; fax: +351-239-78-0552.
E-mail address: lgoncalv@ci.uc.pt (L.M. Gonçalves)

Time for primary review 22 days.

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PII: S0008-6363(99)00358-2

effects on angiogenesis [24] and wound healing [25,26], growth factors have other properties that may have important effects in the setting of AMI. Some growth factors have been shown to be NO-dependent vasodilators [27,28], and some have been reported to have direct neuroprotective [29] and myoprotective effects [30]. Thus, these growth factors could importantly affect the evolution, healing and remodeling of AMI through their effects on systemic hemodynamics and loading conditions, cardiomyocyte protection, angiogenesis, collateral development, and/or wound healing.

Although there are numerous studies of the effects of growth factors in chronic myocardial and limb ischemia [31–33], the potential role of growth factors in AMI has received less attention, and is the subject of this review.

2. Collateral vessels in acute myocardial infarction

The de novo formation of new vessels in the adult organism (angiogenesis), as well as the remodeling of innate collateral vessels (collateral remodeling) are processes that require some time to accomplish. Experiments in animals suggest that both the enlargement of preexisting collaterals and neovascularization require approximately 24 h for the first cellular mitosis [34], and about 3 days for the completion of a functionally relevant collateral circulation [35]. This is confirmed by the finding that collateral flow appears to increase rapidly in the following days after coronary occlusion in the dog. Four days after occlusion, endocardial and epicardial flow have been shown to increase to 50% and 75% of their normal values, respectively [36]. Ten days after coronary occlusion resting flow to the myocardium beyond the coronary occlusion is normal [37].

In humans, initial sprouts are seen 3 days after AMI, shortly after macrophage invasion and before fibroblast proliferation and collagen deposition [38].

Based on this information, therefore, it is difficult to conceive how either angiogenesis or collateral remodeling could play a role in infarct size reduction, given that the myocyte's window of viability is limited to a few hours [39].

From a theoretical point of view, however, vascular development within the myocardial risk region (formation of new vessels and/or the remodeling of innate collaterals) may be beneficial for several reasons. First, when abundant collateral vessels are present within the risk region immediately after the total occlusion of a epicardial vessel, a substantial reduction or even a prevention of the myocardial necrosis can be observed [40]. Second, the development of collateral vessels at the border zone can improve local perfusion and therefore, enhance the function of the ischemic but otherwise viable myocardium in the penumbra of the necrotic area. This may improve left ventricular function and remodeling, both major determinants of prognosis. Third, healing of the necrotic area may not be adequate if the fibroblasts do not receive adequate metabolic support. If the healing process is improved, a reduction in left ventricular remodeling, aneurysm formation and rupture can be expected. These changes may lead to benefit in short and long-term prognosis, as well as functional class.

In patients with an AMI, it has been shown that the extent of preexisting coronary collaterals influences infarct size, the amount of viable myocardium, aneurysm formation, and prognosis [41–44]. In patients after AMI, it has been demonstrated angiographically that collateral development occurs mainly in the area of the necrotic tissue [45,46]. Moreover, the preservation of LV volumes and function after AMI are related to the residual flow obtained by reperfusion or by collateral vessels [47]. In the context of thrombolysis shortly after AMI, the benefits of collateral vessels in the salvage of myocardium is well documented [48–51]. When thrombolysis is not successful, a lower CPK release and a subsequent improvement in LV function can be expected if there is a good collateral network to the ischemic region [48–50].

Despite its well known angiogenic properties [12,13], and the demonstration of an overexpression of VEGF protein and its receptor after AMI [52,53], there are no published studies on the use of VEGF as a potential therapeutic agent in the context of AMI. The growth factors most intensively studied in AMI are the FGFs and IGFs.

During recent years, a number of experimental studies have suggested that treatment with angiogenic growth factors can promote the development of collaterals to ischemic tissue in models of progressive coronary occlusion [16–19], and AMI [20–22].

3. Fibroblast growth factors

3.1. Molecular characterization

The FGF family of growth factors is comprised of at least eighteen distinct, but structurally related, growth factors. All members contain a common domain which is responsible for most of their structural homology. FGF-1 and FGF-2 are the most widely studied members of the FGF family.

3.2. Acidic fibroblast growth factor (FGF-1)

FGF-1, also called acidic FGF, is a 140 amino acid peptide [54]. The three-dimensional structure of FGF-1 has recently been shown [55]. Slightly shorter and longer forms of FGF-1 have also been identified [54]. FGF-1 gene has been cloned and expressed [56]. FGF-1 and FGF-2 have a 55% amino acid sequence homology. This suggest that they both derived from a common ancestral gene [57].

However, FGF-1 and FGF-2 are formed from two different genes in two different chromosomes, which can be explained by gene duplicating and evolutionary divergence [57].

3.3. Basic fibroblast growth factor (FGF-2)

The peptide of FGF-2 (basic fibroblast growth factor) has been purified and sequenced, and its gene been cloned and expressed [58]. Southern blot analysis demonstrates that FGF-2 is encoded by a single gene [59]. The single-copy gene for human FGF-2 (*FGFB*) has been localized on chromosome 4 [60]. The three-dimensional structure of FGF-2 has been elucidated [55].

A comparison of the FGF-2 human and bovine nucleotide and amino acid sequences show a high degree of conservation. Only two of the 155 amino acids are different, giving an overall amino acid sequence homology of 98.7% [61]. The high degree of protein sequence conservation suggests a very strong selection pressure for conservation of function and structure.

The final protein is formed by 146 amino acids after removal of the amino-terminal extension of nine amino acids [54]. There are no precursors with an extended carboxyl terminus because a termination codon directly follows the codon for amino acid 146 [58]. The amino-terminal region of FGF-2 has been demonstrated to function as a nuclear translocation sequence. These residues do not specifically interact with the remainder of the molecule, and if removed, do not induce a loss of function [62].

Multiple molecular forms of FGF-2 have been reported [63]. These proteins are synthesized from one mRNA species, and some initiate translation at non-AUG codons [63]. Human FGF-2 is expressed in four forms: an 18 kDa (155-amino acid) form generated by initiation at the AUG codon, and 22, 22.5 and 24 kDa forms (196, 201, and 210-amino acids) arising from the CUG codons located upstream of the conventional AUG start site [63]. The high molecular forms of FGF-2 contain the complete amino acid sequence of the 18 kDa form in addition to NH_2-terminal extensions of varying lengths.

The N-extension of FGF-2 confers a nuclear localization signal [64], and increases FGF-2 nuclear localization which usually is associated with cell proliferation [65]. The FGF-2 molecular heterogeneity is further complicated by the fact that FGF-2 isolated from tissues is sometimes truncated by enzymatic degradation. For example, FGF-2 has been found as a 131-amino acid form in the ovary, kidney and adrenal tissue, as a 146-amino acid protein in the brain and pituitary, and as a 157-amino acid protein in the placenta [66,67].

Basic FGF has numerous properties that could come into play in the setting of AMI. In addition to its effects on angiogenesis [24] and wound healing [25], basic FGF has been shown to be a moderately potent NO-dependent vasodilator [27], and has been reported to have direct neuroprotective [29] and myoprotective [30] properties.

4. Insulin growth factors

4.1. Characteristics

Insulin growth factors (IGFs) I and II, also known as somatomedins [68], were shown to be survival factors to motor neurons [69]. IGF-I gene expression in mammals typically results in multiple mRNA species ranging in size between 0.7 and 7.6 kb [70]. IGF-I and II are single-chain polypeptides usually of 7.5 kDa [68]. IGF-I and IGF-II are, respectively, 70 and 67-amino acid proteins [68]. IGF-II is thought to play an important role in fetal growth and development. The human IGF-II gene is situated on chromosome 11, very close to the insulin gene [71].

There is a 62% amino acid homology between IGF-I and IGF-II molecular structures [68].

High concentrations of IGF-I and II show insulin-like metabolic characteristics in vitro and in vivo [68].

These growth factors have an important role in controlling the proliferation, differentiation and metabolic activity of mesodermal cells [68].

IGFs can attach not only to binding proteins (IGFBP) that are thought to regulate their biological action and bioavailability [72], but also to insulin receptors, and type 1 or 2 IGF receptors [68].

IGF-I has been shown to be an angiogenic growth factor as potent as FGF-2 in promoting rabbit corneal angiogenesis [73]. Moreover, IGF-I seems to participate in the healing process [74].

4.2. FGFs and acute myocardial infarction

Franco et al. [23] was the first to report on the effects of FGF-2 in AMI. In his cat model, AMI was induced by occlusion of the left anterior descending artery (LAD). FGF-2 (25 μg) was suspended in Sephadex beads and injected directly into the ischemic myocardium, 2 min after coronary occlusion. The authors claimed that infarct size was reduced with this treatment, and speculated that this effect was mediated by myoprotective effects of FGF-2.

Using a canine proximal LAD ameroid model, Banai et al. [18] reported a 44% incidence of AMI. Three weeks after ameroid placement, a sponge saturated with FGF-1 (1–800 μg) was interposed between a vascular pedicle and the epicardium in the LAD territory. They reported that myocardial perfusion was not significantly increased in treated dogs; however, striking vascular smooth muscle cell hyperplasia was evident in arterioles and small arteries, exclusively in areas of subendocardial infarction. In some areas smooth muscle cells hyperplasia was extreme, causing occlusion of the vessels. This result probably was

a consequence of the high local level of the growth factor achieved in the myocardial tissue.

Yanagisawa-Miwa et al. [20] administered intracoronary FGF-2 (10 μg) into the left circumflex coronary artery (LCx), 30 min and 6 h after LAD occlusion in dogs. The LAD occlusion was induced by the delivery of an artificial thrombus to a segment of the coronary artery previously made stenotic by laser thermal injury. One week later, there was a reduction in infarct size (5% vs. 20%), a better LV ejection fraction (94% vs. 45% from baseline), and an increase in the number of capillaries and arterioles in the FGF-2-treated animals, without any significant deleterious hemodynamic effects. These authors hypothesized that the angiogenic response was the cause of myocardial salvage. However, this is unlikely, given that the first division of endothelial cells requires nearly 24 h after the onset of ischemia [75,76] and 2–3 days are required after FGF-2 administration for the formation of new capillaries [77,78]. In dogs, it is known that the necrotic process is almost completely established after 4 h of ischemia [39]. Therefore, it is highly unlikely that the angiogenic effect can have had any significant role in the reduction of necrosis. Yanagisawa-Miwa et al. [20] did not report the spontaneous rate of LAD recanalization in the first hours after AMI.

In another study, Battler et al. [21] induced focal MI in pigs by embolizing sustained-release beads containing FGF-2 (0,12 μg/kg) into the distal LAD. Thus, the growth factor was immediately available at sites of focal infarction. Increased vascular number was observed in FGF-2-treated animals at day 14. There was no evidence of improvement in LV function as evaluated by echocardiography. The sizes of the risk regions and zones of necrosis were not reported, but were probably small given that no deaths or arrhythmias occurred in either group, and no significant changes in blood pressure were observed in the control group after the induction of AMI.

Uchida et al. [22] induced AMI in dogs by embolizing 0.1 ml of inorganic mercury into the LAD. The dogs were randomized into four experimental groups: saline; heparin (3 mg), FGF-2 (30 μg) or FGF-2 (30 μg)+heparin (3 mg). These drugs were administered into the pericardial cavity through the right atrium using a thin needle-tipped catheter. In this study they did not report the time of administration of the drugs after coronary occlusion. The authors considered this procedure to be relative safe, because they did not observe any tamponade, even in dogs that received heparin. One month later, they observed a significant reduction in myocardial necrosis and an improvement in LV function in FGF-2-treated dogs. This benefit was even greater in dogs treated with FGF-2 plus heparin. These changes were correlated with changes in vascular number. No deaths were reported. The vasodilatory properties [27] of FGF-2 may have had a confounding effects on the results. Vasodilatation could have allowed the mercury to migrate distally in the coronary circulation, reducing the risk region in FGF-2-treated animals. Risk region was not reported in this study.

Miyataka et al. [79] administered 300 μg of FGF-2 directly into the myocardium supplied by the LAD just before the coronary occlusion in dogs. Myocardial perfusion was reported to be enhanced 4 weeks after occlusion in the subendocardial, midmyocardial, and subepicardial regions in FGF-2-treated animals. However, this difference was only seen when the data was presented as ischemic zone/normal zone ratio. In absolute terms, there were no difference. There was less necrotic myocardium in the ischemic region as well as less fibrosis in the FGF-2-treated animals [79]. The authors reported 50% mortality in both groups. This may have induced a selection bias towards dogs with higher values of myocardial perfusion. In this study, both necrosis and fibrosis were reported as subjective scores.

In a rabbit model, Hasegawa et al. injected 100 μg of FGF-2 into the myocardium supplied by the LAD, prior to acute occlusion [80]. There was subjectively less fibrosis and more viable myocardium in the border zone in FGF-treated animals; however, microsphere perfusion within the infarcted area was not enhanced. Interestingly, increased perfusion was observed in the noninfarcted area of FGF-treated rabbits. The reasons for this are unclear.

Watanabe et al. [81] induced an AMI in pigs by placing an embolization coil in the distal LAD. Four to five weeks later each animal was injected in eight nearby myocardial points with FGF-2 alone (10 μg), or FGF-2 combined with heparan sulfate, heparin, or beads. From these eight injection points four were placed in the normal myocardium and four at the border zone. FGF-2 angiogenic potential was evaluated 4–5 weeks after injection. An increased number of vessels was detected, particularly after FGF-2 plus heparin treatment. These data are difficult to interpret because the different treatment regimens were tested in the same animal in adjacent areas of the myocardium. Some of these agents may have had interfering actions in adjacent regions.

Scheinowitz et al. [82] gave intraperitoneal FGF-2 in rats, starting immediately after AMI, continuing for a duration of one week. Six weeks after AMI, LV cavity diameter was smaller and wall thickness was larger in FGF-2-treated animals, outside the necrotic zone [82]. In a similar study, the same group reported that intraperitoneal FGF-2 administration was not associated with changes in left ventricular geometry [83].

These studies are summarized in Table 1.

4.3. FGFs and reperfusion

Using an in vitro model Padua et al. [84] demonstrated that FGF-2-perfused hearts (5–20 μg/heart) exhibited increased resistance to ischemia-reperfusion injury. FGF-treated hearts also showed improved functional recovery after ischemia-reperfusion injury. This study was the first

Table 1
Studies of FGF-2 in acute myocardial infarction[a]

Authors	Animal model	Vascular bed	Delivery	Dose	Necrosis reduction	Increased number of vessels/perfusion
Franco et al. [32]	Cat	LAD	IM	25 μg	Yes	NR
Yanagisawa-Miwa et al. [20]	Dog	LAD	IC	10 μg (2X)	Yes	Yes
Battler et al. [21]	Pig	LAD	IC	0.12 μg/kg	NR	Yes
Uchida et al. [22]	Dog	LAD	IPc	30 μg	Yes	Yes
Miyataka et al. [79]	Dog	LAD	IM	300 μg	Yes	Yes
Hasegawa et al. [80]	Rabbit	LAD	IM	100 μg	Yes	Yes
Watanabe et al. [81]	Pig	LAD	IM	10 μg	NR	Yes
Scheinowitz et al. [82,83]	Rat	LAD	IPt	500 μg	NR	NR

[a] IM=Intramyocardial; IC=Intracoronary; IPc=Intrapericardial; IPt=Intraperitoneal.

to demonstrate a cardioprotective effect of FGF-2, similar to that previously reported with neuronal cells [85].

Using a canine model in which 4-h mid-LAD occlusion was followed by reperfusion, Horrigan et al. [86] demonstrated reduction in infarct size in FGF-2-treated animals (10 μg infused intracoronary twice, 10′ after occlusion, and just before reperfusion). FGF-2 treatment was not associated with beneficial effects on ejection fraction, hemodynamic improvement, or evidence of neovascularization. Several unexpected findings were reported in this study. The necrotic area (expressed as a percentage of the risk region) in the control group was particularly low (28%) 4 h after occlusion. (Usually between 75–90% of the myocardial tissue inside the risk region is necrotic 3 h after coronary occlusion [39]). No coronary vasodilatory effects were found after the intracoronary administration of up to 100 μg of FGF-2. This is in contradistinction to another report that showed that FGF-2 is a coronary vasodilator in dogs [24].

In addition to necrosis, a number of myocytes undergo apoptosis during ischemia-reperfusion injury. In post-mortem studies in humans that died shortly after AMI, apoptotic myocytes were frequently found after successful thrombolysis [87]. Cuevas et al. [88] suggested in rats (20 min of ischemia+24 h of reperfusion) that the apoptotic process triggered by ischemia-reperfusion injury is reduced after FGF-1 administration (both native FGF-1 and a non-mitogenic isoform), shortly after the induction of the ischemia [88].

Htun et al. [89] studied the effects of FGF-1 and FGF-2 in pigs subjected to LAD occlusion for 45, 60 or 90 min, followed by 120 min of reperfusion. These animals were divided into nine experimental groups. These authors suggested that local intramyocardial infusion of FGF-1 (0,5 μg/ml, 20 ml/min) and/or FGF-2 (2 μg/ml), 60 min before the occlusion of the LAD was associated with a protection similar to that obtained by ischemic preconditioning. This effect was receptor-mediated and also required the mitogenic portion of the FGF molecule [89]. Moreover, FGF-1 and FGF-2 administration did not prevent cell necrosis, but only delayed the process doubling the time necessary for complete infarction.

These studies are summarized in Table 2.

4.4. IGFs and acute myocardial infarction

In patients with AMI, increased IGF-1 levels have been associated with improved left ventricular remodeling and function [90]. Based on experimental animal studies, however, the role of IGF-1 in myocardial remodeling is less clear. Using a transgenic mouse model overexpressing IGF-1B in cardiac myocytes, Li et al. [91] demonstrated that constitutive expression of IGF-1 prevented necrosis of viable myocardium after AMI, reducing ventricular dilation and improving myocardial loading and hypertrophy. In a study in which IGF-1 protein was administered to rats with AMI, there was no apparent effect on left ventricular geometry [83].

There are also suggestions that IGF-2 may improve regional cardiac function by inducing regional myocardial hypertrophy in peri-infarct areas [92]. In a recent study, severely dysfunctional myocardium (after MI) was found to undergo additional hypertrophy and functional improvement in response to IGF-1 [93].

Table 2
Studies of FGFs in coronary occlusion/reperfusion

Authors	Animal model	Vascular bed	Delivery	Dose	Necrosis reduction
Padua et al. [84]	Rat	Global	Perfusate (in vitro)	5–20 μg	Yes
Horrigan et al. [86]	Dog	LAD	Intracoronary	10 μg (2X)	Yes
Htun et al. [89]	Pig	LAD	Intramyocardial	2 μg/ml	No

4.5. IGFs and reperfusion

Insulin growth factor I (IGF-I) as well as IGFBP-3, IGFBP-5 and IGFBP-6, seem to participate in inflammation-linked angiogenesis and/or tissue repair [14,15]. Insulin growth factor II (IGF-II) and IGFBP-5 (which interferes with IGF action, decreasing its function) are upregulated by ischemia-reperfusion and also by surgical stress. IGFBP-5 appears 30 min after IGF [94], a period of time coincident with the ''window'' in which the myocardium is protected by preconditioning.

Vogt et al. [95] used a pig coronary occlusion model followed by 120 min of reperfusion. Using this model, the intramyocardial injection of IGF-II (0,25 μg/ml, over 60 min) delayed the onset of MI. This effect is similar to that of insulin administration, which results from insulin receptor activation and is prevented by IGFBP-5 and lavendustin A, a tyrosine kinase protein inhibitor.

In a rat model of myocardial ischemia (20 min) and reperfusion (24 h), Buerke et al. [96] demonstrated that 1–10 μg IGF-I given 1 h before coronary occlusion was associated with decreased necrosis as evidenced by creatine kinase loss and neutrophil accumulation in the ischemic area. IGF-I also decreased the incidence of myocyte apoptosis in this model [96].

5. Study limitations

In all AMI studies analyzed in this review, coronary occlusion was induced in unconscious animals. The presence of anesthesia and, in particular, the surgical preparation of these animals, create many problems that importantly confound the interpretation of the studies [97]. Anesthetics may have major effects on arterial and venous tone, determinants of LV loading conditions. The effects of anesthetics on BP, heart rate and contractility have important effects on myocardial oxygen demand. Anesthetics and invasive surgery have profound effects on autonomic tone, which impacts on many determinants of infarct size.

Some of the reviewed studies did not report infarct size as a percentage of the risk region [20,22,23,79,89]. The major determinants of infarct size are risk region size, followed by myocardial perfusion to the ischemic region, and rate–pressure product [97]. Risk region is a critical baseline characteristic that is dependent on anatomical considerations. Therefore, the baseline assessment of risk region size, as well as the presentation of the infarct size as a percentage of the risk region, is fundamentally important for accurate comparisons of the efficacy of agents for infarct size reduction [97].

Measurement of risk region with vital dyes several days after coronary occlusion can be associated with a significant error [86]. Because collateral development occurs naturally after coronary occlusion, it is likely that substantial collateralization of the border zone occurs within a few days after coronary occlusion [35]. Such collaterals will allow the vital dyes to penetrate much further into the risk region than at time zero, resulting in underestimation of the risk region.

Macroscopic measurement of infarct size [20,22,23,86,89,95] may also be a source of error. Although less expensive and labor intensive, positive staining with tetrazolium is not synonymous of myocyte viability [97]. Moreover, macroscopic analysis is not able to identify the complex microscopic interdigitations between infarcted and normal myocardium [97].

In some of the reviewed studies, the number of myocardial vessels was assessed in the absence of perfusion-fixation [20–22]. Under these circumstances, many vessels may be missed.

In one study [21], heparin was administered with the growth factor. Heparin is a known angiogenic factor [98–100], and may have influenced the final result in this particular study. Heparin can be indirectly angiogenic by inducing the liberation of growth factors from the extracellular matrix [101], preventing the inactivation of growth factors [102] and increasing half-life [103], and by potentiating the mitogenic activity of growth factors [104].

In two studies [22,81], the statistical results were not Bonferroni corrected, overestimating the level of significance obtained.

6. Future research directions

Our understanding of the role of angiogenic growth factors on AMI is still in its infancy. More studies are needed to further clarify the role FGFs and IGFs on myocardial protection, remodeling, healing, and angiogenesis. Study of the potential roles of additional growth factors such as VEGF, TGFs, angiogenin, and HGF in the AMI setting is also warranted.

7. Conclusions

In conclusion, published data suggest that FGFs and IGFs may modestly reduce infarct size after AMI. It is unclear whether these effects are due to direct support of angiogenesis, myocyte protection, salutary hemodynamic changes, or effects on apoptosis. The studies are generally limited in size, and in many cases technical factors obfuscate appropriate interpretation of the results. The effects of various growth factors in AMI should not be generalized across agents, and the effects of a specific agent in the setting of AMI may differ significantly from its effect in occlusion/reperfusion. Additional studies in this field are warranted.

Acknowledgements

I thank Dr. Ellis Unger for his reading of this paper and his helpful editorial suggestions.

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