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A Review on the Characteristics of Tissue Culture Bioreactors Used For the Development of Small Diameter Artificial Cardiovascular Grafts

Jafarihaghighi F[1], Ardjmand M[1*], Bahramib H[2] and Mirzajanzadeh M[1]

[1]Department of Chemical Engineering, South Tehran Branch, Islamic Azad University, Tehran, Iran

[2]Department of Mechatronics, Arak University, Iran

***Corresponding author:** Mehdi Ardjmanda, Head of Department of Chemical Engineering, South Tehran Branch, Islamic Azad University, Tehran, Iran, Tel: +989121513117; E-mail: m_arjmand@azad.ac.ir

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1. Abstract

The technology of bioreactor is crucial for Tissue Engineering (TE). They can provide an in vitro environment mimicking in vivo situations for the growth of tissue substitutes. Also, they enable systematic studies of the responses of living tissues to various biochemical and mechanical cues. The various types of bioreactors develop for tissue-specific applications. The expansion of the functional and suitable substitute for small diameter (<6 mm) displacement is challengeable. TE can show a new horizon for damaged vessels and heart by using bioreactors. Although vascular surgery and artificial devices could show developments for heart disease, they have some defection. They cannot remodel, grow, or repair in vivo. In the current review, we summarise and highlight the benefits of the main types of bioreactors used for cardiovascular tissue engineering. Also, we show the comparison between the bioreactors, current challenges, and the future trends for producing suitable cardiovascular tissue replacements.

2. Keyword: Bioreactors; Tissue engineering; Cardiovascular; Artificial vein; Small diameter

3. Introduction

The loss or defection of tissues is the main problem of morbidity and mortality in countries [1]. The significant budget spendson implant devices every year [2]. The high risk of infections and graft rejection are essential challenges for tissues substitution and allograft materials [3]. There are numerous restrictions for artificial implants which make them improper for using. The limited lifespan, insufficient bonding, and allergic reactions are some issues for artificial implants [4, 5].

The primary effect of atherosclerosis is on the small, medium, and large size of arteries [6, 7]. Many reasons for diseases such as gangrene, aneurysms, and stroke and so on is that [8, 9]. The excessive deposition of lipids has made the categorized of atherosclerotic lesions. They surround with SMCs, ECM, and covered with the fibrous cap [10, 11]. All these enable to prevent the flow of blood when becoming large sufficient. The natural vessels apply for patients success merely around 70%. The blood vessel substitutes are suitable for autologous arteries in the peripheral and coronary bypass processes [12-14]. There are some obstacles in these methods because of previous surgery, vessel disease, and trauma [15, 16]. The dimension restrictions, disjunction, mechanical property mismatch are some reasons for failing this method [17]. Coronary Artery Bypass Grafting (CABG) cannot improve the patency rates as synthetic materials [18, 19]. The Dacron® and Teflon® were the first efforts for vessel substitutes. Synthetic material scan achieve some success for larger diameter vessels [20]. In contrast, the use of synthetic materials for the small diameter has some obstacles with tissue–material interfaces and biological interactions. Patency rates of synthetic grafts compared with natural vessels are much lower for small and large diameter [21].

The TE can be a decent way of solving problems by producing in the vitro. The TE can be a great method for restoring the cell-based substitutes. Also, this strategy can improve tissue function. The serious matters of this tactic are related to building large-scale biological products. They should be safe, clinically useful, and financially plausible. The use of bioreactors vanguard role in TE. Cultivating mammalian cells under the domination of bioreactors can show high importance of them for TE [22]. Bioreactors can control several factors such as mechanical forces, pH, and temperature, etc.The ability of bioreactors to supply the physical

Kind	Volume(mL)	Nutrient Media Flow	Pressure	Shear Stress (dyne/cm^2)	Frequency	Time (day)	Reference
Pulsatile perfusion	-	-	-	-	-	6-11	[56]
T Flask & Spinner Flask	50 spinner flask	-	-	-	40rpm spinner flask	28 and 49	[57]
Dynamic rotating	50	-	-	0.3 to 0.8	5rpm	-	[58]
Pulsatile flow	-	9.6 (mL/min) after 3 days	100 (mmHg)	-	30 to 120 (beats/min)	14	[59]
Pulsatile flow	300	Static & constant & pulsed flow	80-120 (mmHg)	-	0.5 (Hz)	49 and 63	[60]
Pulsatile flow	400	-	270/-30 (mmHg)	-	-	56	[61]
Pulsatile perfusion	700	50-1000 (mL/ min)	80 for diastole & 120 for systole (mmHg)	0.067-13.5	1-5 (Hz)	28	[62]
Pulsatile perfusion	-	-	-	9.9 in diastole & 13.2 in systole	60 (cycle/ min)	35	[63]
Flow-deformation	-	-	220 (Mbar)	-	1 (Hz)	-	[64]
TPS	125	2 (mL/min)	NG	0.6	-	14	[65]
Dual-mode	50	-	0-420 (mmHg)	-	0.5 (Hz)	5	[66]
RWV	250	-	3.02 (Pa) & 8.95 (Pa)	-	5 & 20 (RPM)	14	[67]
Custom designed vascular	-	20 to 60 (mL/ min)	10 for static & 60 for dynamic (mmHg)	-	-	7	[68]
pulsatile perfusion	-	8 & 40 (mL/ min)	-	-	1 (Hz)	4 to 11	[69]
Custom-made decoupling	50	0-70 (mL/min)	5.3 (KPa)	0 - 5 (Pa)	0-5 (Hz)	10	[70]

Table 1. Different types of bioreactors have been used in the studies

and biochemical regulatory signals make them be agood candidate for new tissues [23].

Bioreactors can apply for various objectives regarding TE [24]. Design of bioreactors is muchcrucial in TE. They can use for cell proliferation, production of 3D tissue constructs, etc. The control of environmental statutes is much imperative to design bioreactors. Moreover, bioreactors should permit for automated processing steps. Also, precise key criteria for 3D tissue constructs based on scaffolds and cells should mind. They consist of mechanical stimulation, nutrient supplement, cells proliferation, and seeding on scaffolds [25]. The assembling of bioreactors should be simple and quick [26]. They should keep products sterile and effective in tissue forming a short time. Materials must be nontoxic or definite tissue types [27]. They should sterilize for using again. Sensors need for bioreactors for monitoring culturing situations, and pumps must be precise in producing mechanical stimuli [28].

This review provides a critical discussion of the various types of bioreactors which applied for generating small diameter. The importance of bioreactors is often neglected, wefocus on specific stimulation requirements for effective bioreactors, pointing out future challenges in the development of next-generation bioreactors for clinical usage, and benefits of adopting bioreactors in the clinical strategies.

4. Bioreactors

Bioreactors play a leading part in tissue engineering and procedures [25, 29]. The bioreactors which are used in tissue engineering, have affected the biological processes [30-34]. Bioreactors enable use for various functions such as artificial tissue formation, scaffold fabrication, proliferation, and cell culture. Also, they can prepare control of the physiological situation as electrical stimulation. Bioreactors cancontrol the mechanical stretch and continuous media perfusion for development and maturation of 3D artificial tissue are another ability for bioreactors[35].

Different type of bioreactors which used in TE are included spinner flask [36-38], rotating wall [39-41], compression [42], strain [43], hydrostatic pressure [44-46], flow perfusion [33, 46-50] , combined bioreactor [51, 52] and pulsatile flow reactor [53-55].

All the bioreactors which applied in TE had three types of flow situations. Laminar, static, and turbulent flow use in these studies. The cell type and origin for reaching proper results are essential. Also, some factors such as different shear stress and mass transfer rates, nutrient media flow and so forth for culturing cells play a pivotal role in the results. (Table 1) shows the diverse factors of TE bioreactors which applied in small diameter in different studies.

5. Static Culture

The main advantage of the static culture is that they can design and operate easily. This type of bioreactor has some restriction in the nutrient diffusion with large constructs. One of the restrictions includes both internal and external mass transfer are taken on by diffusion [65]. The shear stress in this type of system is very low. Statically cultured constructs normally contain a heterogeneous structure and also composition. They comprise the necrotic central region. They also include the dense layers of viable cells encapsulating the construct outer edge. The concentration gradients and accumulation of waste materials are the prime cause of this situation [25, 65, 66, 69, 71, 72].

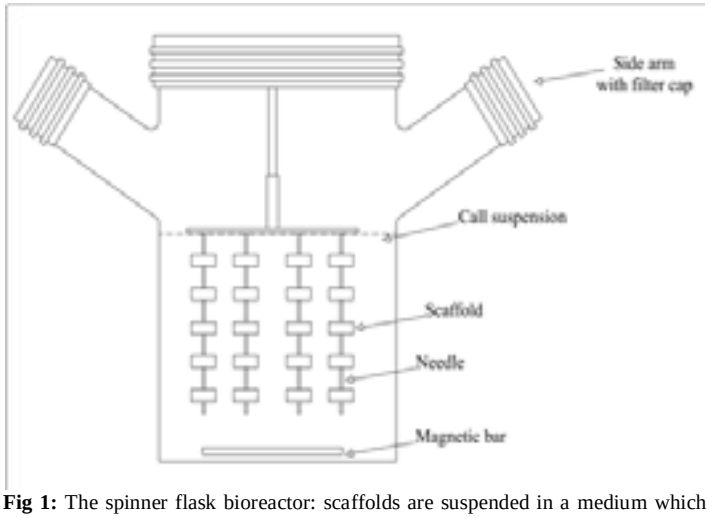

Fig 1: The spinner flask bioreactor: scaffolds are suspended in a medium which the medium stirred applying the magnetic stirrer to develop nutrient transfer to the scaffold

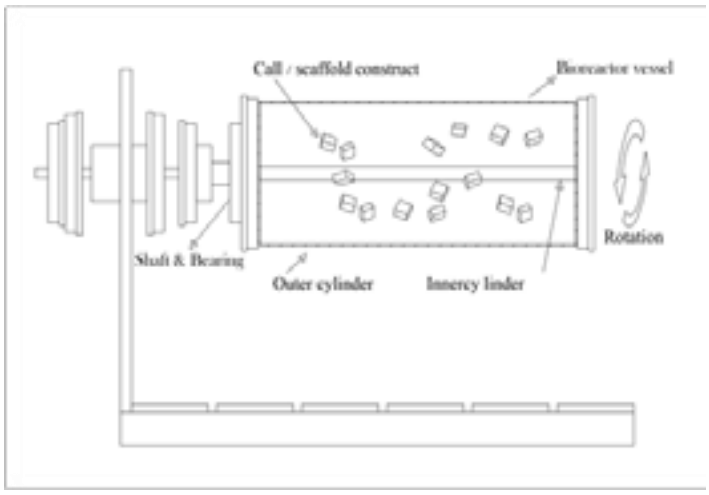

Fig 2: The rotating wall vessel bioreactor: the scaffolds are suspended in the medium owing to the drag forces and opposing gravitational.

6. Spinner flasks

Generally, the continuous stirred tank reactors are applied in bioprocess and also spinner flasks bioreactors (Fig. 1). These reactors employed in TE are preceded from them [73-75]. Scaffolds hang at the end of needles which locate in the culture media flask (in spinner flask). The media blend by the magnetic stirrer and also with regard to the movable fluid. Also, scaffolds stabilize in position. Flow through the surface of the scaffolds, and this makes eddies in the surface pores of scaffolds. They are related to turbulent flow and transitional, and eddies affect the amount of fluid which

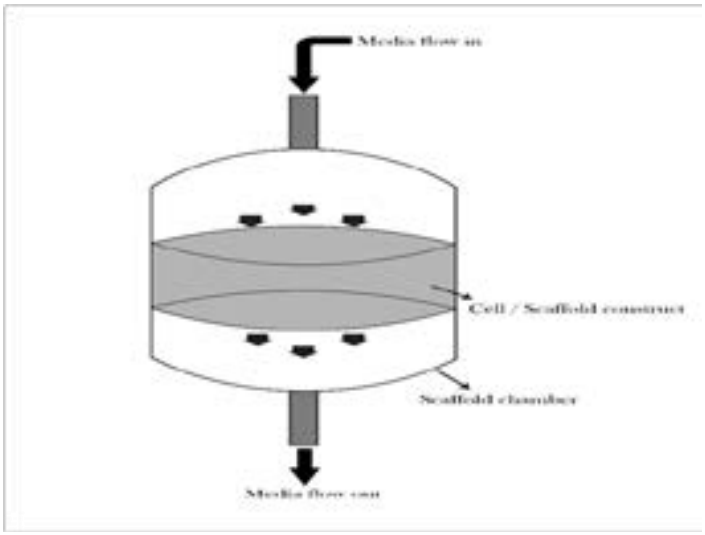

Fig 3: An example of perfusion bioreactors which can be applied for seeding

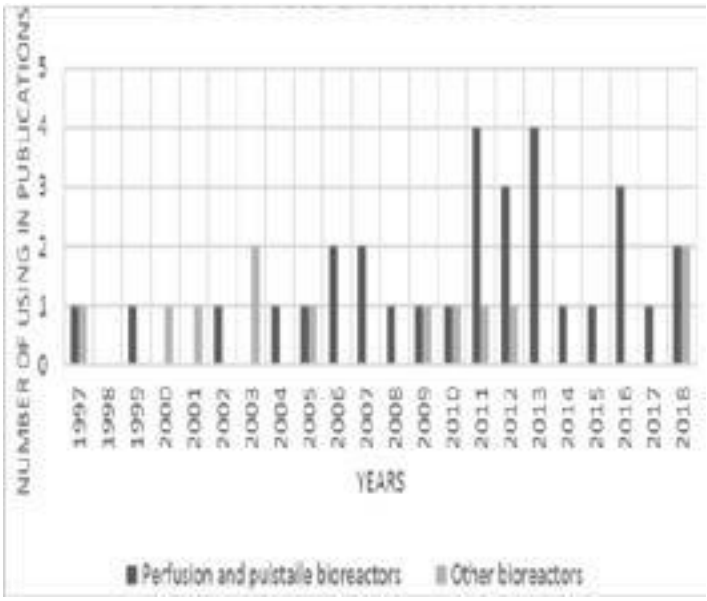

Fig4: Comparing the frequency of use of the bioreactors in papers over the years

conveys to the scaffold's center [76, 77]. The capacity of spinner flasks is roughly 120 ml, however up to 8-liter flask. They drive at 50–80 rpm and also 50% of the medium which employed in them alter every two days [78]. The homogeneous cell distribution from scaffolds and cells mainly settle on the building periphery cannot transfer by mass transfer in spinner flask [76]. The spinner flasks are superior to cultivate under static situation for cardiac constructs and cartilage cultivation. The reason is that they can prepare better mixed-environment for the cell and also reduce the static cell layer which situates in construct surface [79, 80]. The optimal situation may not occur for spinner flasks due to the superior shear stress and turbulent flow. They provoke the outer fibrous capsule shape in cartilage tissue which matures in normal spinner flasks [81]. Wavy-walled bioreactors which are a modified spinner flask are designed due to the increase of the axial blending in the low level of shear stress. They demonstrate smooth waves imitate baffles [82]. They can raise matrix deposition and cell proliferation [75, 83, 84]. Stirred flask bioreactors can develop assembly and cell survival on many surfaces. These developments in stirred flask bioreactors appear with construct cultivation [85-87]. The milieu of stirred flask makes the promotion of cell proliferation and development of nutrient diffusion. El Haj et al. indicated to heterogeneous shear forces which prohibited homogenous tissue expansion [72].

In the study of Kim et al. the agitating and stirring methods illustrated high seeding densities. The efficiency of seeding in the stirred system was inferior to the agitated technique. Kim et al. showed cells grew faster on the surface of matrices. They promoted the lower cellularity and decrease cell distribution in the construct of static-cultured tissue compared to stirred-cultured. The stirred bioreactor increased nutrient transport, and this had affected the poor tissue expansion with a static culture. Also, stirred bioreactor made the cells grew uniformly over the construct which this influenced high cellularity and uniform cell distribution [57].

7. Rotating wall vessel

The shear stress is critical in regulating mechanical properties for tissue manufactures. Due to this, the demand for bioreactors with low shear stress appear due to that emergence of unsought capsules around the tissues [81]. NASA introduced and expanded the Rotating Wall Vessel (RWV) which was able to preserve cell culture over space shuttle blast off and landing from high forces. By these advantages, they could use for tissue engineering (Fig. 2) [88]. The privilege of this type of bioreactor is that they have low shear stress. The RWV gives the liberty to scaffolds and can move in media and put in the vessel [89, 90]. Scaffolds suspend by the rotation of the walled vessel in media because the rotation caters the balance condition for hydrodynamic drag force with gravitational force. The system distributes homogeneous cell more than static culture. Also, the fluid conveyance increases in the same procedure to spinner flasks mechanism [76]. The rotation of bioreactors is around 15-30 rpm and during the growth of tissue. The speed should be raised because of scaffold suspension and gravitational force balance. The gas interchange happens through a gas exchange-membrane [91]. The RWV bioreactors can promote external mass transfer which is under the laminar flow situation [92]. The characteristic exterior tissue layer can grow with dynamic laminar flow and the fibrous capsule is not shaped. The diffusional transfer of oxygen is the restriction for this bioreactor. The shear stress levels can decrease by the dynamic laminar flow in RWV in contrast with stirred flasks [93].

Xing et al. could show the high ability of RWV bioreactor for the nutrient infiltration. The expression of the SMC specific genes, calponin, and α-smooth muscle actin in the hMSCs considerably developed in the bioreactor. The graft fabrication time diminished remarkably by RWV bioreactor and premade ECM [67].

8. Novel bioreactor

Some novels strategy applied by several studies. Nasseri et al.

employed the hybridization oven in their paper. They evaluated the effectiveness of the rotation on cells culturing. Also, seeding on tubule-shaped polymer scaffolds. The privilege of the partial rotation of the freely moving constructs made uniform shear stress distribution. The medium velocity for inner and outer construct was another advantage for the partial rotation. The hybridization oven defection was the lack of gas exchange in culture vessels which made altered the medium every day[58].

Dvir et al. applied the novel bioreactor which could cultivate the multiple 3-dimensional cellular constructs in a flow chamber. This bioreactor could cultivate the modular of multiple cellular constructs of different sizes which at a total cross-section of 20 cm^2. Also, the bioreactor can prepare equal shear and fluid flow along a bioreactor cross-section. The design of the nets holding cell constructs in a perfusion bioreactor aided the maximal exposure to the culture medium [94].

The reactor of Bachmann et al. could use the long-term conditioning of the human endothelial cells and interact with synthetic materials under the dynamic combinations (wall deformation and wall shear stress). Both supraphysiological and physiological range achieved for the wall deformation and wall shear stress values. Bachmann et al. could prove suitable optical conductivity of a system which allowed online monitoring of cell actions[64].

The ability of a bioreactor for the subsequent and fabrication in vitro stimulation in the single device indicated by Bono et al. They could prove that the mechanical situation enhanced both the matrix re-organization and gel compaction. Their results represented the enhancement of cell density in the strained instances and the high homogeneous transmural cell growth [66].

The bioreactor of Ma et al. could enhance the proliferation and adhesion of the ECs. This bioreactor could hinder seeded ECs from washing away afterward transplantation in an arterial system. This outcome showed dynamic seeding led to ECs to tightly attach to decellularized aortae of fetal pigs. The main issues of the bioreactor were simulated the in vivo vascular and culture effectiveness of the grafts [68].

9. Perfusion bioreactor

The perfusion bioreactor (Fig. 3) enablesto apply for pulsatile and non-pulsatile flows which are in a Cardiovascular Engineered Tubular Construct (CETC). Also, this type of bioreactor expands by the closed loop perfusion system. The pump, chamber, and tube are the apparatus of perfusion bioreactor [95, 96]. The outside and inside CETC perfusions are two types of system, and the third structure has consisted of pressure transducers and digital camera. The system can cater to the gas supply, high sterility and coordinating for standard humidified incubator by high isolate cell-culture environment. Sterilizing with ethylene oxide is possible for bioreactor, and this gathers by a standard screwdriver [97]. The CETC what is cannulated (by demountable male luer locks) on both ends which use for inner diameter which is between 2 mm and 6 mm. The altering flow rate is happened by the peristaltic pump which enhances average static pressure in the construct. The reservoirs situate in the temperature bath for temperature control. Thelevel of CO2 is titrated to obtain proper pH which is related to the culture medium. The structure of the culture chamber is transparent polycarbonate which coating with gasket [97]. The procedure of the watertight chamber makes the longitudinal strain's periodical altering over mechanical situations. Chesler et al.[98] Indicated that a damping reservoir eliminated and T-connector added with an extra 60 cm of tubing for pulsatile flow. The digital TV camera and two pressure transducers used for CETC biomechanical control and they join the computer. The inquiry of CETC burst strength and the recording of the relevance between pressure and CETC radius was allowed by this system. Several studies applied perfusion bioreactor and could significant outcomes.

The bioreactor of Niklason et al. prepared pulsatile flow to the four bioreactors. Niklason et al. expanded the system under the situation of pulsatile intraluminal pressure for culture vascular prostheses to approach mimic vivo condition. The vascular tube cultured and seeded with SMCs for 6 and 11 days.Culturing for 11 days presented higher tissue mass present for this time with this bioreactor. They could increase the tube's physical strength more than a static culture. However, the vascular tissues could not tolerate arterial pressures. They could decrease the time of culturing to 2 months compared to L'Heureux et al. [56, 99].

Buijtenhuijs et al. showed that the period of dynamic culturing in a bioreactor.They displayed proper scaffolds stability and the absence of bacterial or fungal contamination. The SMC cultured under the pulsatile flow environments gained average systolic, wall shear rate, diastolic pressures, and pressure waveforms analogous to situations in the human carotid artery. The tissue formation improved compared with static circumstances when the SMC culturing in the tubular scaffolds. The greater homogeneous distribution of the SMC all over the scaffolds and upper collagen mRNA appearance levels found under dynamic compared with static situations.The mRNA expression levels of the apoptosis and proliferation markers displayed the better cell numbers in scaffolds culturing under dynamic circumstances could be elucidated by improving cell proliferation. Their results could prove that the consumption of glucose and lactate formation with cells illustrated the higher aerobic cell metabolism under dynamic compared with static situations [59].

The pulsed flow-stretch bioreactor was superior to over single graft bioreactors which proved by Syedain et al. The leading reason was that it could let for the similar growth milieu which led to high elimination among matured grafts. They could measure the graft burst pressure by calculating stiffness at the range of 80 and 120 mmHg in the bioreactor. The bioreactor could cater transmural flow to the culture medium which was on both surfaces and made nutrients homogeneous distribution. The data revealed the importance of cyclic stretching for the vascular graft. It related to pulsed flow over in bioreactor culture, enhanced circumferential tissue and collagen concentration which connect with graft strengthening [60].

The number of privileges represented by the pulsatile bioreactor of Huang et al. The bioreactor could construct a physiological pulsatile milieu with employing cyclic radial strain to vessels in the culture and biochemical surrounding of native blood vessels. The multiple vessels engineering what could culture concurrently under various mechanical situations in a controlled chemical milieu were another advantage. The bioreactor also could show that the EC monolayer simply coated on the engineered vessels luminal side for animal implantation samples and culturing in different diameter size (from 1 mm to 3 mm). They indicated the bioreactor was constantly regenerated vessels which displayed mechanical properties and authorized fruitful implantation tests in animal models [61].

Diamantouros et al. reached (at 80–120 mmHg) pressure ranges in contrast of previous studies for reconstruct physiological outlines or conveyance greater rate pulses [100, 101]. The compliance measurement played a crucial role in their system due to that the combination of optical micrometer and transparent cultivation chamber permitted accurate on-line amounts of the vessel diameter from the compliance and improved them. The system's capability to employed pressure pulses into supra-physiological frequencies was displayed proper durability tests [62].

Ahn et al. referred to the bioreactor could be preserved cell sheets viability. The results could demonstrate the improved cell survival of multilayered cell sheets. However, more cell sources were needed to acquire sufficient cells to employ the tubular scaffolds constructs. Ahn et al. displayed the production of denser scaffolds with increment protein expression pulsatile bioreactor. It was related to SMCs contractile features and also meantthe thickness of the SMC sheet. The data could show the enhancement of tissue maturation by mechanical stimulation with pulsatile perfusion bioreactor earlier to transplantation [63].

The bioreactor of Melchiorri et al. reached the low-level shear stress. Their bioreactor could control the flow through the grafts as well as conveying the fluid shear stress on the EPCs and influencing the cellular proliferation and differentiation. Their results could depict the robust platform for the population progress and function for the dynamically cultured TEVGs compared with the static milieu in the low shear stress milieu. The significant enhancement of the DNA content and cell illustrated the bioreactor was superior to the static culture situations. This enhancement could grow the population growth and cell proliferation [65].

The dynamic pulsatile perfusion could impact on the smooth muscle lineage for rapidly establishing in the study of Lin et al. They proved the multipotent cell differentiation into the smooth muscle lineage characterized by improvement expressions of the SM-specific marker, smooth muscle myosin heavy chain, as well as, smooth muscle alpha-actin compared to the static culture by pulsatile stimulation in the bioreactor. The enhancement of the synthesis of tropoelastin was shown by the bioreactor cultivation. It was the extracellular cross-linking in the elastic fiber compared to the static culture [69].

Haaften et al. employed the independently combine these two sorts of mechanical cues in the eight parallel vascular grafts. They indicated that the numerous levels of cyclic stretch and shear stress were distinguished and made the system validated experimentally and computationally. Haaften et al. referred that the contribution of the shear stress overruled the stretch-induced cell proliferation as well as the matrix production. Whereas, both kinds of hemodynamic loading resulted in cell alignment. At the macroscopic level, they indicated the cyclic stretching resulted in the supreme linear stress–stretch response and this did not connect to the attendance of the shear stress [70].

10. Conclusion and Future Trend

Coronary heart disease is the principal cause of deaths attributable to cardiovascular disease. Thus, the importance of the solution for this concernis at the central global debate. Bioreactors have been applied for all aspects of the small diameter and make us one step closer to improve the tissue in vitro for a large-scale medical application. Tomovement the comparatively small diameter tissue engineering, development must make in both physical and chemical fields. Among all the physical contexts, the main priority should be the development in the field of bioreactors. Since the main process of cultivation in these beds is carried out. The most significant bioreactors were pulsatile and perfusion bioreactor (Fig. 4) in recent studies. This type of bioreactor can operate capacity for control of flow rate, longitudinal strain VTE graft with high accuracy and pressure. Numerous study referred to the mechanical situation in the peripheral direction which is catered by perfusion apparatuses and applied internal pressure over construct maturation. The fluid transport by flow perfusion bioreactors is superiortothe rotating wall and spinner flask bioreactors with the same scaffolds and flow rate. Also, the distribution of cells-changed is conditional on bioreactors. Histological analysis depicted that the bioreactor of flow perfusion culture ended in uniform cell distribution entirely the scaffolds and the same results for the rotating wall vessel. This bioreactor can potentially remove mass transfer restrictions. Perfusion bioreactors can show superior control of mass transfer compared to other conventional systems. The pulsatile perfusion bioreactors have been expended to imitate cardiovascular situation in the in vitro due to that vascular cells represented the pulsatile physical forces over vasculogenesis and all over the life. The perfusion procedure prepares intraluminal pulsatile flow for reactors. Pumps apply the pressure accompanied by changeable stroke volume in which the range of pulse rates

can operate by bioreactor. The pulsatile conditions can use for bovine vascular cells, small diameter vascular grafts, and heart valve which the results are acceptable. Periodic extension of an extremely elastic membrane produces media's pulsatile flow. It is deflated and inflated with the air pump. The endothelial cells and vascular fibroblasts seed in polymeric scaffolds which grow under gently enhancing pressure situation and nutrient media flow. The SMC culture into porous tubular scaffolds can employ in this type of system. These dynamic situations can be provided waveforms pressure, diastolic and systolic pressures and medium shear rate which analogous with human carotid artery situation. The enhancement of nutrient transport is another the benefits of perfusion bioreactors. They can provide mechanical stimuli to the cells by forcing the culture medium via pores of the solid porous 3D scaffolds. These advantages can prove that the perfusion bioreactor has a suitable culture environment and great potential to produce cartilage grafts or vascular grafts of clinically relevant size. The enormous benefits of perfusion bioreactors have increased usage in the last decade as shown in (Fig. 5) which makes it a good choice for future studies.

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